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[Intervention Review]

Prone position for acute respiratory failure in adults

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ABSTRACT

Background

Acute hypoxaemia de novo or on a background of chronic hypoxaemia is a common reason for admission to intensive care and for provision of mechanical ventilation. Various refinements of mechanical ventilation or adjuncts are employed to improve patient outcomes. Mortality from acute respiratory distress syndrome, one of the main contributors to the need for mechanical ventilation for hypoxaemia, remains approximately 40%. Ventilation in the prone position may improve lung mechanics and gas exchange and could improve outcomes.

Objectives

The objectives of this review are (1) to ascertain whether prone ventilation offers a mortality advantage when compared with traditional supine or semi recumbent ventilation in patients with severe acute respiratory failure requiring conventional invasive artificial ventilation, and (2) to supplement previous systematic reviews on prone ventilation for hypoxaemic respiratory failure in an adult population.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 1), Ovid MEDLINE (1950 to 31 January 2014), EMBASE (1980 to 31 January 2014), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to 31 January 2014) and Latin American Caribbean Health Sciences Literature (LILACS) (1992 to 31 January 2014) in Ovid MEDLINE for eligible randomized controlled trials. We also searched for studies by handsearching reference lists of relevant articles, by contacting colleagues and by handsearching published proceedings of relevant journals. We applied no language constraints, and we reran the searches in CENTRAL, MEDLINE, EMBASE, CINAHL and LILACS in June 2015. We added five new studies of potential interest to the list of "Studies awaiting classification" and will incorporate them into formal review findings during the review update.

Selection criteria

We included randomized controlled trials (RCTs) that examined the effects of prone position versus supine/semi recumbent position during conventional mechanical ventilation in adult participants with acute hypoxaemia.

Data collection and analysis

Two review authors independently reviewed all trials identified by the search and assessed them for suitability, methods and quality. Two review authors extracted data, and three review authors reviewed the data extracted. We analysed data using Review Manager software and pooled included studies to determine the risk ratio (RR) for mortality and the risk ratio or mean difference (MD) for secondary outcomes; we also performed subgroup analyses and sensitivity analyses.

Main results

We identified nine relevant RCTs, which enrolled a total of 2165 participants (10 publications). All recruited participants suffered from disorders of lung function causing moderate to severe hypoxaemia and requiring mechanical ventilation, so they were fairly comparable,

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given the heterogeneity of specific disease diagnoses in intensive care. Risk of bias, although acceptable in the view of the review authors, was inevitable: Blinding of participants and carers to treatment allocation was not possible (face-up vs face-down).

Primary analyses of short- and longer-term mortality pooled from six trials demonstrated an RR of 0.84 to 0.86 in favour of the prone position (PP), but findings were not statistically significant: In the short term, mortality for those ventilated prone was 33.4% (363/1086) and supine 38.3% (395/1031). This resulted in an RR of 0.84 (95% confidence interval (CI) 0.69 to 1.02) marginally in favour of PP. For longer-term mortality, results showed 41.7% (462/1107) for prone and 47.1% (490/1041) for supine positions, with an RR of 0.86 (95% CI 0.72 to 1.03). The quality of the evidence for both outcomes was rated as low as a result of important potential bias and serious inconsistency.

Subgroup analyses for mortality identified three groups consistently favouring PP: those recruited within 48 hours of meeting entry criteria (five trials; 1024 participants showed an RR of 0.75 (95% CI 0.59 to 94)); those treated in the PP for 16 or more hours per day (five trials; 1005 participants showed an RR of 0.77 (95% CI 0.61 to 0.99)); and participants with more severe hypoxaemia at trial entry (six trials; 1108 participants showed an RR of 0.77 (95% CI 0.65 to 0.92)). The quality of the evidence for these outcomes was rated as moderate as a result of potentially important bias.

Prone positioning appeared to influence adverse effects: Pressure sores (three trials; 366 participants) with an RR of 1.37 (95% CI 1.05 to 1.79) and tracheal tube obstruction with an RR of 1.78 (95% CI 1.22 to 2.60) were increased with prone ventilation. Reporting of arrhythmias was reduced with PP, with an RR of 0.64 (95% CI 0.47 to 0.87).

Authors' conclusions

We found no convincing evidence of benefit nor harm from universal application of PP in adults with hypoxaemia mechanically ventilated in intensive care units (ICUs). Three subgroups (early implementation of PP, prolonged adoption of PP and severe hypoxaemia at study entry) suggested that prone positioning may confer a statistically significant mortality advantage. Additional adequately powered studies would be required to confirm or refute these possibilities of subgroup benefit but are unlikely, given results of the most recent study and recommendations derived from several published subgroup analyses. Meta-analysis of individual patient data could be useful for further data exploration in this regard. Complications such as tracheal obstruction are increased with use of prone ventilation. Long-term mortality data (12 months and beyond), as well as functional, neuro-psychological and quality of life data, are required if future studies are to better inform the role of PP in the management of hypoxaemic respiratory failure in the ICU.

PLAIN LANGUAGE SUMMARY

Prone (face-down) position for mechanical ventilation of adults with acute respiratory failure

Review question

This review sought to investigate whether face-down ventilation could improve important outcomes by, for instance, reducing the death rate (mortality) among individuals requiring mechanical ventilation in intensive care. We also wanted to identify disadvantages and complications associated with prone positioning, as well as long-term benefits.

Background

People who are admitted to an intensive care unit and need assistance with breathing provided by a ventilator (mechanical ventilation) because of lung damage caused by illness have a high risk of dying. Lungs that are affected by conditions such as pneumonia will consist of normal and abnormal or diseased areas. Recovery of diseased areas takes time, and a person may need support with ventilation while this occurs. Ventilation support is potentially lifesaving, as it maintains proper oxygen levels in the blood while removing carbon dioxide waste. However, the ventilator itself can cause inflammation and thus additional lung complications. The harder a ventilator has to work to achieve normal oxygenation and removal of carbon dioxide, the more likely it is that healthy, normal areas of the lung may be damaged, and the person's condition made worse. Ventilation with the person lying face-down (prone) instead of face-up (supine) might improve how well the ventilator works, thereby reducing these undesirable side effects.

Study characteristics

We identified and included in this review randomized controlled trials of adults that compared conventional mechanical ventilation in the face-down versus the face-up position.

Key results

Reports from nine trials of 2165 participants (10 publications) show that prone ventilation did not appear to be of benefit for all participants requiring ventilation but identified some situations in which it may improve survival. One group of participants with the most severe lung damage appeared to have reduced mortality, as did participants who received treatment early and for prolonged periods. Complications were described. The most common of these were pressure sores and tracheal tube blockage or obstruction. Low blood pressure and abnormal heart rhythms were also seen. Clinicians need to be aware of these and to take preventative actions when possible. The application of prone position to all participants in intensive care who have low oxygen levels is not warranted, but some particular groups of participants, for example, those with especially low oxygen levels, would benefit from prone positioning. Further clinical trials would

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assist in clarifying potential benefits for such patient groups but further trials may not take place because of the very large treatment benefit observed in the most recent clinical trial of participants with very low oxygen levels. In the absence of new trials, meta-analysis of individual patient data may facilitate further assessment.

Quality of the evidence

The quality of the evidence for primary outcomes of this systematic review was low as a result of serious inconsistency and important potential bias.

The evidence is current to 31 January 2014. We reran searches in CENTRAL, MEDLINE, EMBASE, CINAHL and LILACS in June 2015. Five new studies of potential interest were added to the list of "Studies awaiting classification" and will be incorporated into formal review findings during the review update.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Mortality: prone position compared with supine for acute respiratory failure in adults requiring mechanical ventilation in intensive care

Mortality: prone position compared with supine for acute respiratory failure in adults requiring mechanical ventilation in intensive care

Patient or population: adults with acute respiratory failure
Settings:
Intervention: mortality: prone position compared with supine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Mortality: prone position compared with supine				
Short-term mortality (STM) Alive or dead Follow-up: 10 to 30 days	**Study population**		**RR 0.84** (0.69 to 1.02)	2117 (8 studies)	⊕⊕⊝⊝ **Low**[a,b]	
	383 per 1000	**322 per 1000** (264 to 391)				
	Moderate					
	450 per 1000	**378 per 1000** (310 to 459)				
Longer-term mortality (LTM) Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.86** (0.72 to 1.03)	2141 (8 studies)	⊕⊕⊝⊝ **Low**[a,b]	
	470 per 1000	**404 per 1000** (339 to 484)				
	Moderate					
	525 per 1000	**452 per 1000** (378 to 541)				
Subgroup analysis of longer-term mortality: severe hypoxaemia Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.77** (0.65 to 0.92)	977 (7 studies)	⊕⊕⊕⊝ **Moderate**[a]	
	547 per 1000	**421 per 1000** (356 to 503)				

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	Moderate				
	653 per 1000	**503 per 1000** (424 to 601)			
Subgroup analysis of longer-term mortality: lower tidal volume ventilation Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.73** (0.55 to 0.96)	911 (5 studies)	⊕⊕⊕⊖ **Moderate**[a]
	451 per 1000	**329 per 1000** (248 to 433)			
	Moderate				
	523 per 1000	**382 per 1000** (288 to 502)			
Subgroup analysis of longer-term mortality: ARDS only Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.85** (0.71 to 1.01)	1758 (8 studies)	⊕⊕⊕⊖ **Moderate**[a]
	483 per 1000	**411 per 1000** (343 to 488)			
	Moderate				
	522 per 1000	**444 per 1000** (371 to 527)			
Subgroup analysis of longer-term mortality: ≥ 16 hours/d prone Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.77** (0.61 to 0.99)	1005 (5 studies)	⊕⊕⊕⊖ **Moderate**[a]
	470 per 1000	**362 per 1000** (286 to 465)			
	Moderate				
	526 per 1000	**405 per 1000** (321 to 521)			
Subgroup analysis of longer-term mortality: enrolment ≤ 48 hours after entry criteria/ventilation Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.75** (0.59 to 0.94)	1024 (5 studies)	⊕⊕⊕⊖ **Moderate**[a]
	469 per 1000	**352 per 1000** (277 to 441)			
	Moderate				
	523 per 1000	**392 per 1000**			

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		(309 to 492)	

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]Blinding of participants and carers was not possible. Researchers also may not have been adequately blinded. All analyses were downgraded because of this important potential bias, leading the quality of all subgroup analyses to be rated as moderate
[b]For the primary outcomes, inconsistency across studies reflected different patient populations, different management strategies generally and differences in adaptations to resulting effects of the intervention. This led to further downgrading of the quality of evidence for the primary outcomes to low
[c]Longer-term mortality = 31 to 180 days OR hospital mortality

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BACKGROUND

Description of the condition

Acute respiratory failure can arise from numerous diseases or disease processes, and is a common reason for admission to hospital. Patients with profound gas exchange abnormalities unresponsive to ward-based strategies (such as oxygen therapy or continuous positive airways pressure (CPAP) for hypoxaemic respiratory failure, or non-invasive ventilation (NIV) for hypercapnic ventilatory failure) may be referred to intensive care units (ICUs) for further management. Patients whose problems are predominantly related to oxygenation include those with pneumonia, pulmonary oedema, pulmonary aspiration pneumonitis and pulmonary thromboembolism. Acute lung injury and acute respiratory distress syndrome (Bernard 2005; MacCallum 2005; Phua 2009; Rubenfeld 2007) are reported in an important group of patients treated for hypoxaemia within the ICU. Acute respiratory distress syndrome (ARDS) is not a single disease and may arise as the result of pulmonary and extrapulmonary disease processes (Walkey 2012), as can its less physiologically severe counterpart, acute lung injury (ALI). Redefinition of ARDS, which has occurred since most studies were designed or published, has seen ALI renamed as "mild ARDS" (ARDS definition workforce 2012). For the new criteria of mild, moderate and severe ARDS, mortality is quoted as 27%, 32% and 45% (ARDS definition workforce 2012). Diffuse alveolar damage is found in only 50% of cases (de Hemptinne 2009), and doubt has been cast on the usefulness of the ARDS paradigm (Marini 2008; Soni 2010). However, the concept is considered useful by most intensivists (Bernard 2005). Patients with ventilatory failure and hypercapnia include those with chronic obstructive pulmonary disease (COPD) and those receiving central nervous system depressant drugs; patients with neuromuscular problems may also require mechanical ventilation.

Thus a wide variety of patients may require mechanical ventilation within the ICU. Variability is great with regards to severity of illness and severity of structural lung damage. The reversibility of disease-driving processes is also inconsistent.

Description of the intervention

Patients with profound hypoxaemia present a significant challenge for carers in dealing with both hypoxaemia and underlying process(es). Although hypoxaemia often is not perceived as the ultimate cause of death in these patients, it does have deleterious effects (Strachan 2001). Avoidance of profound hypoxaemia is one of the goals of supportive therapy in ICU, and a variety of manoeuvres are employed to ameliorate hypoxaemia. These include positive end-expiratory pressure (PEEP), inverse ratio ventilation (IRV), alveolar recruitment manoeuvres, restrictive fluid administration strategies, inhaled pulmonary vasodilators such as nitric oxide and prostacyclin, corticosteroids and neuromuscular blockers and mechanical ventilation in the prone position (Adhikari 2004; Adhikari 2007; ARDSnet 2006b; ARDSnet 2006a; Cranshaw 2002; Klein 2004; Mentzelopoulos 2005; Papazian 2010). All of these therapies have been shown to improve oxygenation, but few have demonstrated a mortality benefit in randomized controlled trials (Diaz 2010; Papazian 2010; Petrucci 2007). Athough a systematic review of high-frequency oscillation (HFO) suggested possible utility in the management of ARDS (Fan 2010; Sud 2013), two trials reported in 2013 have not confirmed benefit (Ferguson 2013; Young 2013). One of these trials was discontinued early because of increased mortality in the treatment group (Ferguson 2013). Extracorporeal membrane oxygenation (ECMO) has been shown to be of benefit (Noah 2011; Noble 2010) but is available only in relatively few specialized centres. Traditional mechanical ventilation, which normally is utilized in supine and semi recumbent patients, while ensuring short-term survival, may also contribute to lung injury and other deleterious effects (Soni 2008). Ventilator-induced lung injury has been demonstrated both in experimental animal models and in human participants; thus mechanical ventilation can perpetuate or accentuate the original injury to the lung and can cause dysfunction of distant organs (Verbrugge 2007). These effects are known as barotrauma, volutrauma and biotrauma.

Under normal circumstances, patients ventilated in ICUs are cared for in the semi recumbent position, often described as the supine position. This supine or semi recumbent position allows better access for carers to provide interventions such as mouth care and airway and vascular access procedures. It is also more appropriate for critical manoeuvres such as cardiopulmonary resuscitation, should this be required. This position is more comfortable for patients and allows them to better interact with their environment when compared with the prone, face-down position.

This systematic review explores the intervention of placing patients in the prone position (face-down) while they are mechanically ventilated for severe hypoxaemic respiratory failure via a tracheal tube.

How the intervention might work

Chatte 1997 and others have showed that ventilation provided with the patient in the prone position could have salutary effects on oxygenation (Gattinoni 2001; Mure 2001). Studies in recent years, in humans and in experimental animal models, have confirmed that the prone position is associated with improved oxygenation in most individuals. More than 70% of patients with lung injury show clinical improvement in oxygenation with prone mechanical ventilation. In a retrospective multi-variate analysis, prone positioning was independently correlated with positive outcomes in patients with ARDS (Venet 2003). The mechanisms by which prone position improves gas exchange include alveolar recruitment, redistribution of ventilation towards dorsal areas that remain well perfused, homogenization of tidal volume distribution and possible improved postural drainage of secretions (Gattinoni 2006; Guerin 2006). Postural drainage has also been suggested to reduce ventilator-associated pneumonia, although theoretically this could spread organisms and inflammatory mediators within lung tissue, leading to increased damage (Graf 2008; Marini 2010). Homogenization of tidal volume distribution may reduce tissue stress/strain and consequently may diminish the well-described injurious effects of mechanical ventilation, thus providing additional benefit over and above that associated with improved oxygenation (Gattinoni 2012; Gattinoni 2013; Mentzelopoulos 2005; Slutsky 2013). Other effects include improvements in haemodynamics (Guerin 2014).

Thus, three phenomena might improve survival among patients (Charron 2011).

- Reduced extent and duration of severe hypoxaemia.
- Reduced propensity to ventilator-induced lung injury.

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- Reduced occurrence of nosocomial or ventilator-associated pneumonia.

Adverse effects associated with the prone position for ventilation most notably include:

- unplanned extubation and risk of an episode of potentially catastrophic hypoxaemia;
- inadvertent bronchial intubation, which will also worsen hypoxaemia and increase risk of barotrauma (e.g. pneumothorax);
- development of pressure sores;
- ocular complications; and
- intracranial hypertension, which can compromise cerebral circulation.

Improved oxygenation with the prone position could allow additional time for lung reparative processes, and, by reducing secondary lung infection or injury, has the potential to accelerate recovery and lessen mortality among adults with acute respiratory failure. Adverse effects and complications related to the prone position might reduce the overall impact of these potential benefits.

Why it is important to do this review

Patients admitted to the ICU with severe hypoxaemia are at high risk for mortality (ARDS definition workforce 2012; Walkey 2012). For example, Phua and colleagues reported overall mortality in the important subset of ICU patients with ARDS of 44% in observational studies and 36% in randomized controlled trials. This rate of mortality does not seem to have been significantly reduced since 1994, when the American-European Consensus Conference redefined ARDS (Phua 2009). Any intervention that reduces mortality, especially one that can be easily implemented at little additional cost, requires adequate exploration.

OBJECTIVES

The objectives of this review are (1) to ascertain whether prone ventilation offers a mortality advantage when compared with traditional supine or semi recumbent ventilation in participants with severe acute respiratory failure requiring conventional invasive artificial ventilation, and (2) to supplement previous systematic reviews on prone ventilation for hypoxaemic respiratory failure in an adult population.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs) that compared conventional modes of mechanical ventilation in the supine or semi recumbent position versus mechanical ventilation in the prone position in adults with acute respiratory failure.

We included unpublished studies and abstracts when identified.

We imposed no language restrictions.

Types of participants

We included studies on adults with critical illness in an ICU setting requiring conventional mechanical ventilation for acute severe respiratory failure.

We excluded studies primarily investigating participants with chronic respiratory impairment such as COPD. This review focused on acute severe respiratory failure.

We excluded studies on neonates or paediatric participants (i.e. younger than 16 years), which are covered separately in updated Cochrane reviews (Balaguer 2012; Gillies 2012).

Types of interventions

We examined interventions comparing conventional methods of ventilation in the supine or semi recumbent position (which could encompass lateral positioning as part of routine pressure care) versus the prone position.

We excluded studies that used primary positions other than supine or semi recumbent.

We excluded rotational therapies provided in the prone position.

We excluded studies comparing conventional prone ventilation versus other experimental modes of ventilation such as high-frequency jet ventilation (HFJV) or high-frequency oscillation (HFO).

Types of outcome measures

We sought information on the following main outcomes.

Primary outcomes

- Short-term mortality (10 to 30 days, or ICU mortality).
- Longer-term mortality (> 30 days, or hospital mortality).

Secondary outcomes

We also sought information on the following.

- Rate of ventilator-associated pneumonia, as defined in the original studies.
- Number of days on a ventilator.
- Length of ICU stay.
- Length of hospital stay.
- Improvement in oxygenation.
- Adverse events.
- Quality of life.
- Economic outcomes.

Search methods for identification of studies

Electronic searches

We searched the current issue of the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 1), Ovid MEDLINE (1950 to 31 January 2014), EMBASE (1980 to 31 January 2014), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to 31 January 2014) and Latin American Caribbean Health Sciences Literature (LILACS) (1992 to 31 January 2014).

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We searched Ovid MEDLINE and EMBASE using the search terms provided in Appendix 1. We used the same search strategy to search CENTRAL, EMBASE and CINAHL within Ovid. Appendix 2 provides the search terms used for LILACS as accessed through the Virtual Health Library..

We reran searches in CENTRAL, MEDLINE, EMBASE, CINAHL and LILACS in June 2015. We added five new studies of potential interest to the list of Studies awaiting classification; we will incorporate these studies into formal review findings during the review update.

Searching other resources

We also searched for studies by:

- handsearching reference lists of previous trials and review articles;
- handsearching books related to critical care and mechanical ventilation;
- communicating with colleagues, particularly published trialists; and
- performing a subject-specific search of the following journals to look for published proceedings abstracts of clinical trials.
  - *American Journal of Respiratory and Critical Care Medicine,* volumes 175 to 189, 2007 to January 2014.
  - *Critical Care*, volumes 11 to 18, 2007 to January 2014.
  - *Critical Care Medicine,* volumes 35 to 42, 2007 to January 2014.
  - *Intensive Care Medicine,* volumes 33 to 40, 2007 to January 2014.

We searched for relevant ongoing trials at the following websites.

- http://www.controlled-trials.com.
- http://www.update-software.com.

Data collection and analysis

Selection of studies

Two review authors (RB and DWN) independently screened and classified all citations as potential primary studies, review articles or others for inclusion. Two review authors (RB and DWN) examined all potential primary studies and decided whether they should be included in the review. We resolved all disagreements by discussion.

Data extraction and management

Two review authors (RB and DWN) independently extracted in duplicate from each study data on methods and outcomes (Appendix 3). A third review author (AS) checked data subsequently entered onto a Microsoft Excel spreadsheet.

Assessment of risk of bias in included studies

We judged study quality on the basis of criteria and mechanisms described in Table 8.5.d by Higgins et al (Higgins 2011a), which were based on:

- adequacy of randomization;
- allocation concealment;
- blinding of participants and investigators;
- blinding of outcome assessment;
- completeness of outcome data;
- selective reporting; and
- other relevant potential bias.

We addressed the impact of methodological quality on results and performed a sensitivity analysis that excluded poorly performing studies by using the above metric. We rated the quality of evidence by using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system (Guyatt 2008; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c), as described below.

Measures of treatment effect

For dichotomous outcomes, we calculated risk ratios (RRs). We used odds ratios (ORs) when outcomes were very small. We used standardized mean differences (SMDs) or mean differences (MDs) as appropriate for continuous outcomes.

Unit of analysis issues

We identified no specific issues.

Dealing with missing data

We did not specify in the original protocol how missing data issues would be managed (Bloomfield 2009).

Assessment of heterogeneity

We measured heterogeneity by using the Higgins test, whereby an I^2 statistic greater than 25% is considered to show significant heterogeneity. This test describes the percentage of total variation across studies that is due to heterogeneity rather than to chance (Higgins 2003). We used a fixed-effect model when the Higgins test showed good homogeneity (low heterogeneity) between studies; otherwise, we used a random-effects model. Higgins has defined an I^2 statistic of 25%, 50% or 75% as low, moderate or high (Higgins 2003). When present, we planned to explore heterogeneity by considering these options listed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

- Avoiding formal meta-analysis when fewer than two studies provided quantitative data for primary outcomes.
- Ignoring heterogeneity.
- Using random-effects meta-analysis.
- Exploring heterogeneity by using prespecified subgroup analyses or meta-regression when we identified sufficient (> 10) studies.
- Excluding studies as part of a sensitivity analysis (Deeks 2011).

Assessment of reporting biases

We used a funnel plot to assess the risk of reporting bias (Higgins 2011a).

Data synthesis

We reviewed data from included studies qualitatively, and then, when possible, we combined data quantitatively by population, intervention and outcome, using Cochrane's statistical software, RevMan 5.3. We based quantitative analyses of outcomes on "intention-to-treat" results (i.e. results based on the intention-to-treat principle). We followed the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* regarding data synthesis. In cases of very substantial (high)

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heterogeneity (Higgins 2003), we would not pool the results to perform statistical analysis. We used a fixed-effect model when homogeneity between studies was good, and a random-effects model when it was not good.

Subgroup analysis and investigation of heterogeneity

We planned to undertake the following subgroup analyses (SGA).

- Duration of daily ventilation in the prone position (< 16 hours/d vs ≥ 16 hours/d). As any benefit from prone ventilation may be a dose (time)-related phenomenon, daily duration of time in that position would appear potentially important.
- Duration of supine ventilation before randomization. As ventilatory-induced lung injury is relatively rapid in onset, any randomized trials and outcomes reporting very limited exposure to supine ventilation before randomization should be identified.
- Outcome according to severity (oxygenation index; PaO_2/FIO_2 ratio or quotient; severity of illness score, e.g. Simplified Acute Physiology Score II (SAPS II)). As patients with more severe lung injury benefit from prone ventilation, this may be an important subgroup to explore. SAPS II and similar scores may indirectly reflect the severity of inciting injury and may be relevant.
- Tidal volume (size of the mechanical breath given to the participant) in relation to body weight has been shown to affect survival and outcomes between high tidal volume (> 10 mL/kg of ideal body weight), moderate tidal volume (8 to 10 mL/kg of ideal body weight) and low tidal volume (≤ 8 mL/kg of ideal or predicted body weight) and will be explored if the data permit. (Actual body weight exceeds ideal or predicted body weight by a mean factor of 1.25 (Bloomfield 2006) and therefore underestimates the standard metric of tidal volume, which is based on ideal body weight.) We considered "ideal" and "predicted body weight" as interchangeable and based on height and sex of participants.
- We analysed studies of acute lung injury (ALI) together with acute respiratory distress syndrome (ARDS) separately from those examining other causes of acute severe hypoxaemic respiratory failure.
- We further subclassified acute lung injury and ARDS into pulmonary and extrapulmonary causes and as conditions that may behave differently with different ventilatory strategies (Walkey 2012; Ware 2000). We planned to explore differences in outcomes in these subcategories if collected data allowed.

We explored evidence of substantial heterogeneity in primary outcomes as indicated by the Higgins test by performing subgroup analyses, and, if we identified more than 10 primary studies, by performing meta-regression (Deeks 2011). We did not employ statistical techniques for multiple comparisons when conducting these prespecified analyses.

'Summary of findings' tables

We used the principles of the GRADE system (Guyatt 2008; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c) to assess the quality of the body of evidence associated with specific outcomes. In the case of RCTs, the GRADE system allows downgrading of the overall rating of evidence from "high quality" by one or two grades on the basis of study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

We applied the GRADE system to these primary outcome measures.

- Short-term mortality.
- Longer-term mortality.

We also applied this system to four subgroup analyses related to longer-term mortality.

- Participants with severe hypoxaemia.
- Mechanical ventilation with lower tidal volumes.
- Outcomes for participants with ALI or ARDS.
- Maintenance of the prone position for 16 or more hours per day.
- Enrolment within 48 hours of meeting study criteria.

We chose these outcomes for GRADE analysis after the protocol was published, as this tool was not used by The Cochrane Collaboration at that time.

Sensitivity analysis

We undertook a sensitivity analysis of primary outcomes with regards to the quality of data. We excluded from the sensitivity analysis studies with two or more "red flags" for high risk of bias.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We have presented the results of the search as a flow chart (Figure 1). We conducted the main search in April 2012 and updated our search of the same databases from 2012 to January 31 2014. We reran the searches in CENTRAL, MEDLINE, EMBASE, CINAHL and LILACS in June 2015. We found 208 citations and added five new studies of potential interest to the list of Studies awaiting classification. We will incorporate these five studies of interest into formal review findings during the review update.

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Figure 1. Study flow diagram. We reran the searches in CENTRAL, MEDLINE, EMBASE, CINAHL and LILACS in June 2015. We found 208 citations and added five new studies of potential interest to the list of Studies awaiting classification, which will be incorporated into formal review findings during the review update.

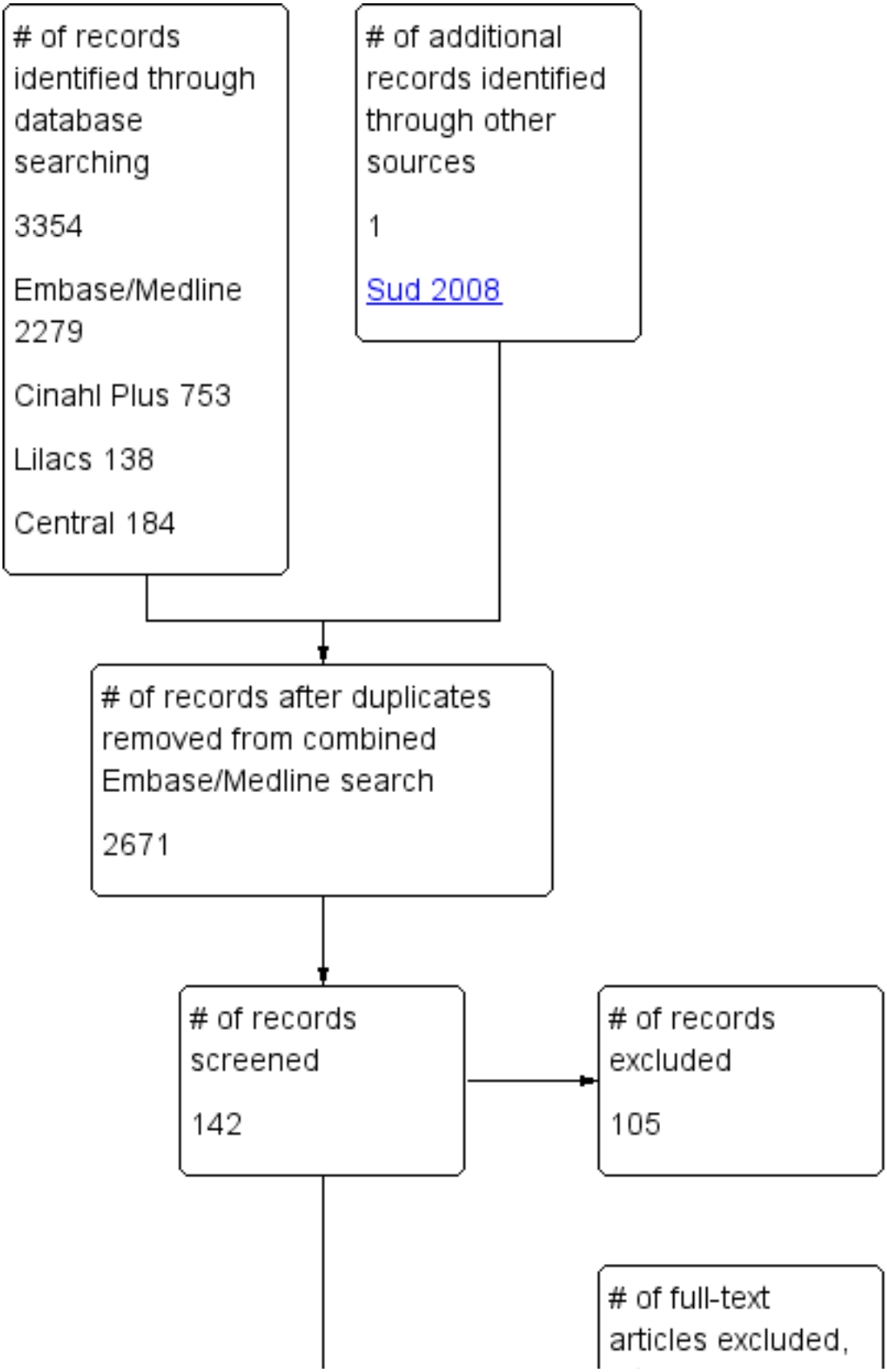

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Figure 1. (Continued)

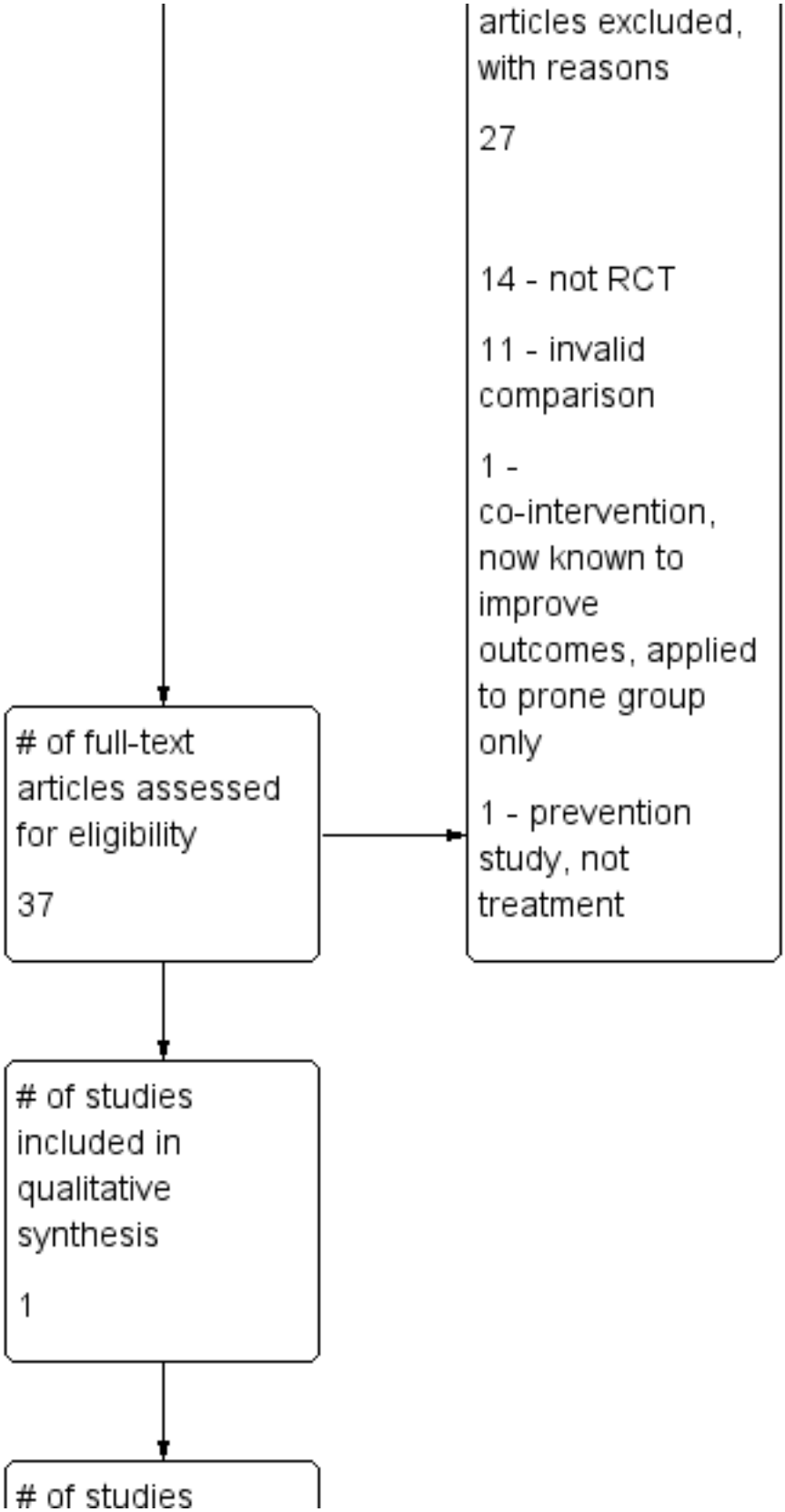

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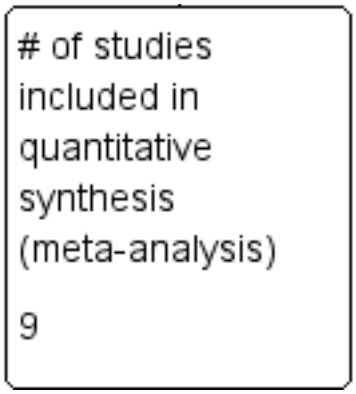
Figure 1. (Continued)



A search of proceedings supplements of the *American Journal of Respiratory and Critical Care Medicine*, *Critical Care*, *Critical Care Medicine* and*Intensive Care Medicine* yielded no additional relevant RCTs.

Included studies

We extracted data from nine primary studies reported in 10 publications. Eight were primary studies published in full form in peer-reviewed journals (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005). One study was reported as an abstract, with supplementary information given in presentation slides provided by Jan Friederich (Leal 1997). We found additional data regarding some of the primary studies in five journal publications (Chiumello 2012; Gattinoni 2010; Sud 2008b; Sud 2010; Sud 2014), which provided additional information on subgroups of participants with very severe hypoxaemia from four studies (Gattinoni 2001; Guerin 2004; Mancebo 2006; Taccone 2009) and on an ARDS subgroup from one study (Sud 2014). Chiumello et al (Chiumello 2012) reported one-year mortality at five of the centres that contributed to the Taccone 2009 study. Sud et al provided additional data regarding severity of illness through SAPS II scores (Sud 2008b). Chiumello reported pulmonary function and quality of life data (Chiumello 2012). Most studies recruited participants with ALI or ARDS, although the largest single study (Guerin 2004) also recruited individuals who would have been excluded from the ALI/ARDS trials, although some information for this subgroup has been made available recently (Sud 2014).

Excluded studies

We excluded five studies that were included in other published meta-analyses. Two studies (Demory 2007; Papazian 2005) investigated the short-term effects of high-frequency oscillatory ventilation (HFOV) in prone and supine participants. One was a prevention study (Beuret 2002), and one (Watanabe 2002) applied an intervention of neuromuscular blockade to the prone group that is associated with improved outcomes (Papazian 2010) and failed to report mortality data. Another study (Curley 2005) included predominantly very young children with a median age of two years and no adults. Two of these studies (Beuret 2002; Watanabe 2002) were conducted in the pre-low tidal volume ventilation era.

Studies awaiting classification

Five studies are awaiting classification (Ayzac 2014; Girard 2014; Hu 2014; Park 2015; Zhou 2014). Please refer to the Characteristics of studies awaiting classification for further information.

Ongoing studies

We identified no ongoing studies.

Risk of bias in included studies

We have graphically presented in Figure 2 review authors' assessment of bias within individual studies, and in Figure 3, bias across studies.

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Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

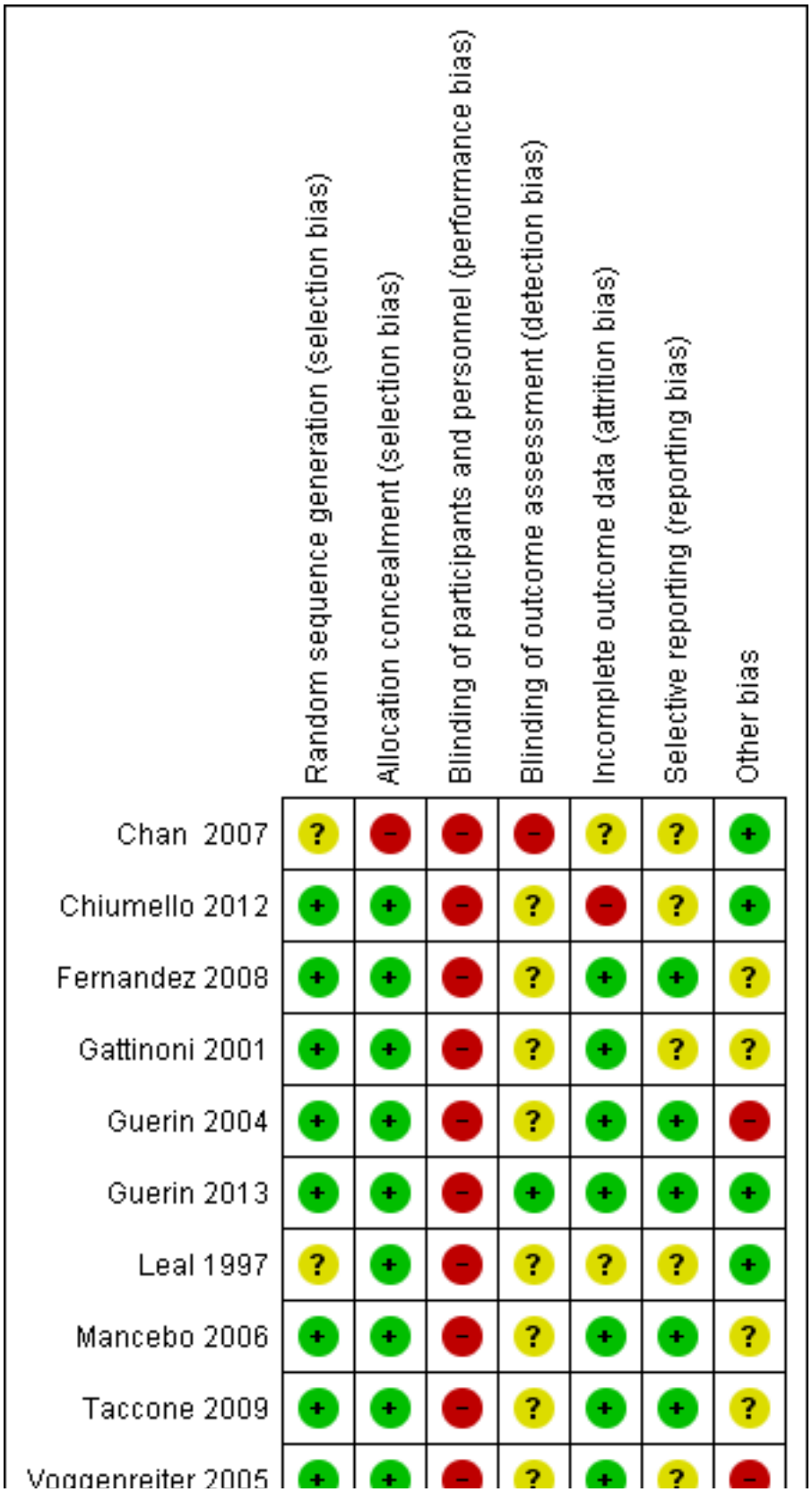

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Figure 2. (Continued)

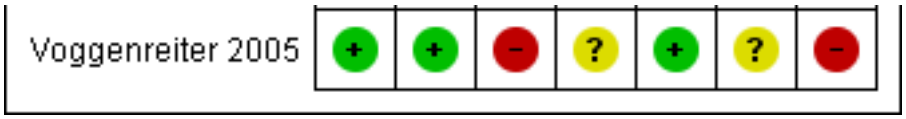
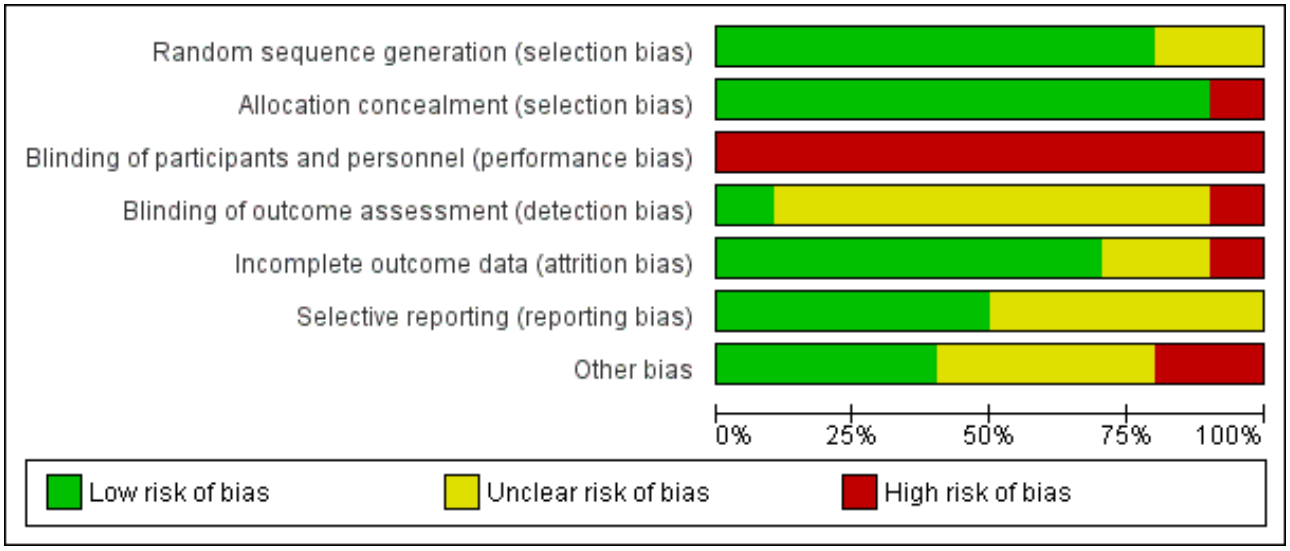


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Allocation sequence generation was of a high standard overall, with most studies employing computer-generated sequences and blinding sequence allocation by using a computer-telephone allocation system of sealed opaque envelopes. Allocation bias seems likely for the study of Chan et al (Chan 2007).

Blinding

Blinding of participants and clinical staff to allocation would be difficult because participants were placed either with face and feet up or with face and feet down. Investigators applied no special measures (whatever they might be) to ensure blinding of participants and staff. Lack of blinding could affect application of important related co-interventions such as decisions on futility, non-escalation of treatment, withdrawal of treatment or continuation of active treatment (Forbes 2013; Morgan 2014; Stapleton 2005; Turnbull 2014). We downgraded the quality of evidence assessed by the GRADE system in all analyses in which it was utilized because important clinical decisions would be made with full knowledge of treatment allocation. It is not clear whether investigators were blind to participant allocation when performing data analyses.

Incomplete outcome data

Most studies reported participants lost to follow-up and used the intention-to-treat principle. Missing data for primary and some major secondary outcomes were small (0 to 5% of participants), and this was unlikely to affect interpretation of findings. However, for some secondary outcomes, the disparity in reporting rates between studies suggests differences in outcome definition, priority for data collection or efforts to minimize these complications.

Selective reporting

Selective reporting within studies was unlikely for the primary outcomes and for subgroup analyses in which death was the outcome of interest. Most studies were conducted at multiple centres, and a pre-study protocol would define criteria for most reported study endpoints. Post hoc analyses might be at risk of selective reporting (e.g. choice of 88 mmHg (11.7 kPa) PaO_2/FIO_2 quotient as cutoff for post hoc mortality subgroup analysis) (Gattinoni 2001).

Other potential sources of bias

For most studies, cross-over of participants from one limb of the study to another was modest. However, cross-over or non-adherence to the protocol was considerable for the study of Guerin 2004. Eighty-one (21%) participants crossed over from supine to prone, and 170/413 (41%) in the prone group were never actually put in prone position, or the prone position was discontinued before the study met prone weaning criteria (Guerin 2004; Sud 2008). This effect would assume even greater importance in subgroup analyses of sicker participants that included an even higher proportion of cross-over participants. Although strictly not bias, this will reduce the efficiency (Lipsey 1990) of a trial and will "silently" increase the risk of type II statistical error. Supplementary per-protocol analysis (Sheiner 1995) would be useful for assessing the impact of cross-overs and of partial and full protocol violations. In addition, one study described differential use of co-interventions (e.g. blood transfusion, neuromuscular blockers) that would be

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expected to influence outcomes (Voggenreiter 2005). Participant losses for main analyses were small (0 to 4.2%), and reasons were detailed. Supplementary analyses were not performed as a result of these small participant losses.

Effects of interventions

See: **Summary of findings for the main comparison** Mortality: prone position compared with supine for acute respiratory failure in adults requiring mechanical ventilation in intensive care

Before the last published trial (Guerin 2013) was included, statistical heterogeneity was low overall, and most analyses had an I^2 statistic = 0. With inclusion of this last trial (Guerin 2013), heterogeneity was substantial, and heterogeneity for the primary analyses moved from 0% without the last study to 60% or greater with inclusion of the last study (Analysis 1.1). Among subgroup analyses of mortality that included data from this trial (Guerin 2013), only one had an I^2 statistic = 0, and the remaining nine analyses demonstrated I^2 statistical values ranging from 39% to 56%. With the last trial of Guerin excluded from the same analyses, all 10 trials had an I^2 statistic = 0 (Analysis 1.3; Analysis 1.4; Analysis 1.6; Analysis 1.9; Analysis 1.11).

For reasons of inconsistency and heterogeneity, the quality of the evidence for primary outcomes based on the GRADE system was downrated further and was classified as low. The option of not exploring and analysing these results was avoided, and a random-effects model was employed. Studies were insufficient to justify meta-regression techniques (Deeks 2011).

Fixed-effect and random-effects models were determined by I^2 statistical value and are presented in the text as appropriate. Presentation of short- and longer-term outcomes in the same forest plot has restricted use of one or the other model for these data pairs, and for some outcomes, minor discrepancies between text and figures may be noted for this reason.

Primary outcomes

Short-term mortality

Eight clinical trials with 2117 participants reported on short-term mortality (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) and were included in this analysis (Analysis 1.1). Overall mortality of participants was 756/2117 (35.7%). Mortality for those ventilated prone was 33.4% (363/1086), and supine 38.3% (395/1031). This resulted in a risk ratio of 0.84 (95% CI 0.69 to 1.02) in favour of the prone position. Before inclusion of the most recent study (Guerin 2013), which exclusively enrolled participants with more severe hypoxaemia than was seen in earlier studies and had a risk ratio for mortality of 0.49, the risk ratio from other studies was close to unity at 0.95. In the Higgins test, the I^2 statistic moved from 0% to 60% with inclusion of the most recent study (Guerin 2013). Visual inspection of the funnel plot was not supportive of major reporting bias (Figure 4). Removal of one study, which applied prone ventilation for only one day (Leal 1997), did not alter the risk ratio, which remained at 0.84.

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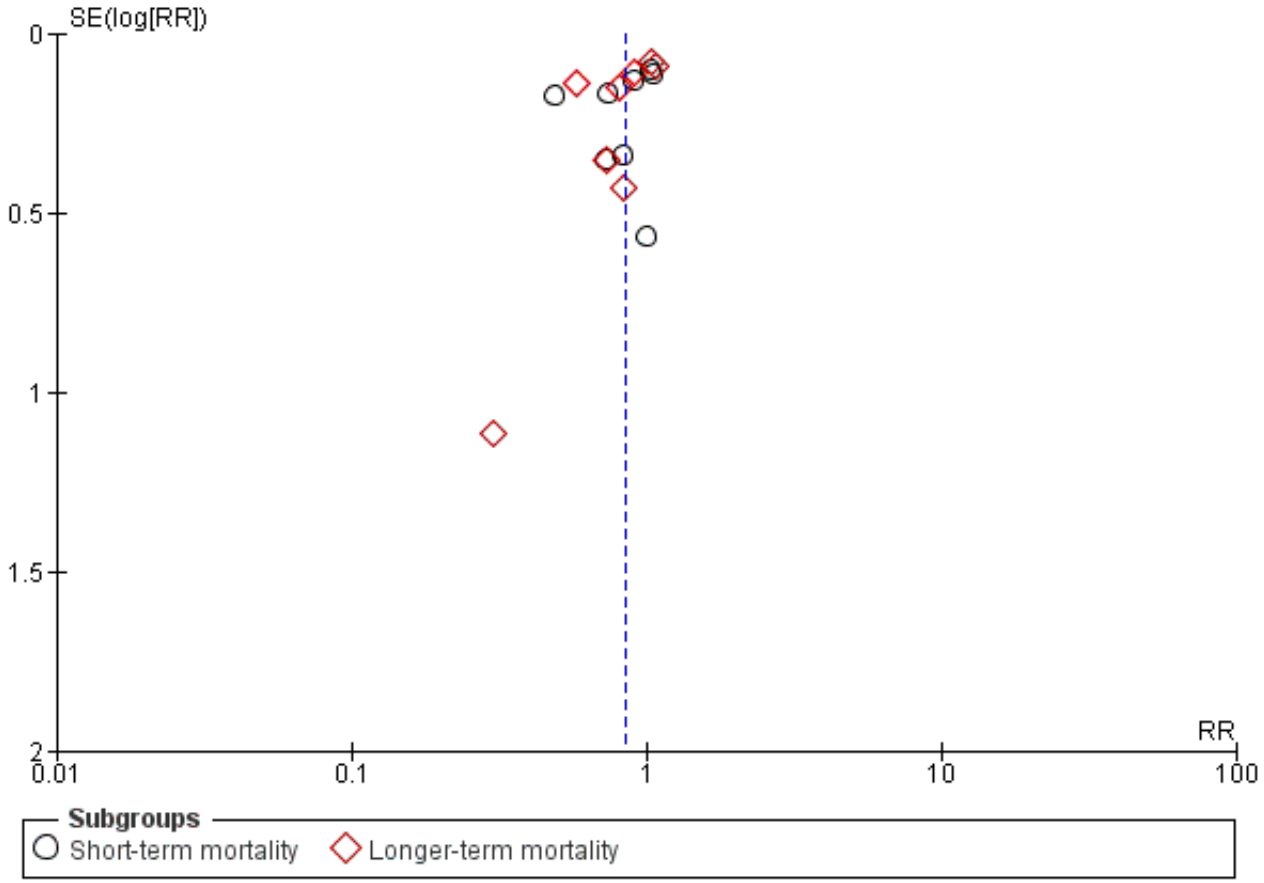
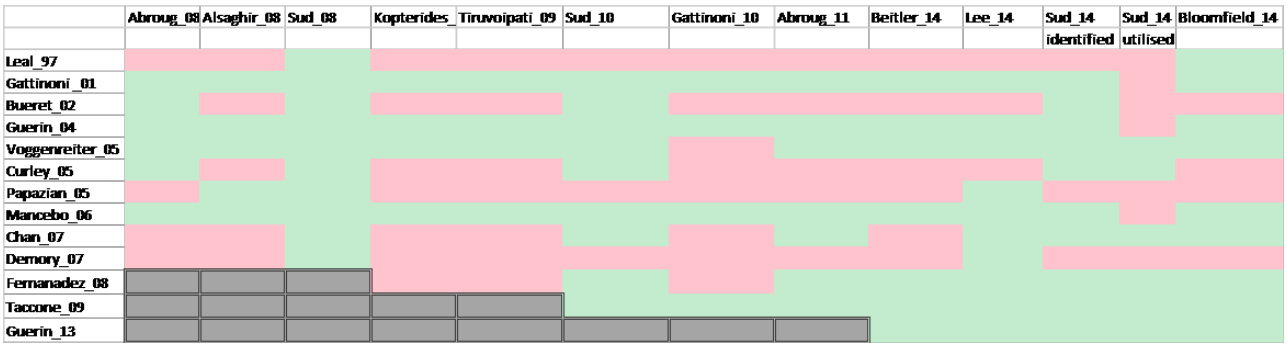
Figure 4. Funnel plot of comparison: 1 Mortality, outcome: 1.1 Mortality.



Longer-term mortality

Eight clinical trials with 2140 participants (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005) reported on longer-term mortality (952/2140), which overall approximated 44.5% (Analysis 1.1). Mortality for prone (462/1099; 42.0%) and supine (490/1041; 47.1%) ventilated participants resulted in a risk ratio of 0.86 (95% CI 0.72 to 1.03) in favour of the prone position. Before inclusion of the last study (Guerin 2013), which had an individual risk ratio of 0.58, the risk ratio from the other studies was again close to unity at 0.97. In the Higggins test (Higgins 2003), the I^2 statistic moved from undetected (0%) to "moderate" heterogeneity at 61%, with the addition of Guerin 2013. Visual inspection of the funnel plot was not supportive of major reporting bias (Figure 5).

Figure 5. Primary studies utilized by systematic reviews (black = not available at time of review; green = utilized; pink = not utilized).



Use of the GRADE system to assess the quality of evidence for major risks of bias from lack of blinding (Guyatt 2011a) and from inconsistency of effect (Guyatt 2011c) reduced the overall rating of evidence quality to "low" for both of these primary outcomes.

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One-year mortality

Only one study (and therefore not part of the quantitative meta-analysis) reported 12-month mortality (113/187) in a secondary publication approximating 60% mortality overall (Chiumello 2012). This population of 187 participants accounted for approximately 55% of the original study population. The point estimate for the risk ratio in this secondary study was 1.13 (95% CI .89 to 1.42) in favour of the supine position in this single-study post hoc analysis.

Results for primary outcomes and for selected subgroup analyses are included in Summary of findings for the main comparison.

Secondary outcomes

Rate of ventilator-associated pneumonia

Five studies (Chan 2007; Fernandez 2008; Guerin 2004; Mancebo 2006; Voggenreiter 2005) reported rates of ventilator-associated pneumonia (VAP), although one study recruiting participants with community-acquired pneumonia reported no cases (Chan 2007), leaving four (1007 participants) for analysis (Analysis 3.1). The overall rate of VAP for participants (226/1007) was 22.4%, and the risk ratio for VAP of 0.88 (95% CI 0.71 to 1.11) favoured the prone position.

Number of days on a ventilator

Three studies (Fernandez 2008; Guerin 2004; Voggenreiter 2005) reported duration of mechanical ventilation in 871 participants (Analysis 4.1). Mean duration of ventilation was reduced by 0.47 days (95% CI -1.53 to 0.59) for participants in the prone position.

Length of ICU stay

Four studies (Fernandez 2008; Guerin 2004; Mancebo 2006; Taccone 2009) with 1309 participants reported ICU length of stay (Analysis 5.1), which was increased for participants in the prone position by a mean of 1.37 (95% CI -1.29 to 4.04) days. Analysis of log (base 10) transformed data provided similar results, with an increase (geometric mean) of 1.07 days for participants treated in the prone position (95% CI -1.3 to 1.5 days).

Length of hospital stay

Only one study (and therefore not part of the quantitative meta-analysis) of 40 participants reported hospital length of stay. This very small study favoured the supine position by a mean of 5.8 (range -7.9 to 19.5) days.

Improvement in oxygenation

Four studies (Gattinoni 2001; Guerin 2004; Mancebo 2006; Voggenreiter 2005) with 827 participants reported improvement in oxygenation (PaO_2/FIO_2 ratio or quotient) over seven to 10 days (Analysis 6.1). The mean difference in improvement in the PaO_2/FIO_2 quotient was 24.6 mmHg (95% CI 13.9 to 35.2 mmHg) compared with baseline measurements at study entry. This equates to 3.3 kPa (95% CI 1.8 to 4.7 kPa) (P value < 0.00001). Variance for two studies (Guerin 2004; Mancebo 2006) was estimated by using the higher of the "paired" variances for the study population. Inflating the entered standard deviations by approximately 50% to 120.0 for these two studies had no impact on inferences. The second study of Guerin (Guerin 2013) was not included in the analysis because of the formal reduction in PEEP mandated by improving oxygenation.

One study (and therefore not part of the quantitative meta-analysis) provided data for the PaO_2/FIO_2 quotient for a very small subset of participants (26) (Chiumello 2012) included in one of the primary studies (Taccone 2009; 342 participants) at 12-month follow-up. PaO_2 data (Chiumello 2012) on air showed a change in the PaO_2/FIO_2 quotient of 43 mmHg (95% CI 15.8 to 70.2 mmHg) in favour of supine ventilation (P value = 0.002). This equates to a PaO_2/FIO_2 quotient of 5.7 kPa (95% CI 2.1 to 9.4 kPa).

Adverse events

Several adverse events were documented across studies and were reported in two different ways: Most studies reported events per participant group, but two studies reported some data as events per participant day. These were analysed separately.

New pressure sores

Three studies (Chan 2007; Gattinoni 2001; Voggenreiter 2005) with 366 participants reported pressure sore events per participant per group (Analysis 7.1), and one additional study of 791 participants and 10,944 event days presented results on pressure sores as events per day. The three studies reported an event rate of 41.3% for participants ventilated prone and 29.7% for those ventilated supine, with a risk ratio of 1.37 (95% CI 1.05 to 1.79; P value = 0.02). The single study (Guerin 2004) reporting events per day (and therefore not part of the quantitative meta-analysis) reported pressure sores on 3.6% of event days in prone groups and 3.0% in supine groups, with an odds ratio of 1.20 (95% CI 0.97 to 1.48; P value = 0.09). Both analyses favoured the supine position to avoid this adverse event.

Tracheal tube displacement

Eight studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Taccone 2009; Voggenreiter 2005) of 2021 participants provided information on tracheal tube displacement or accidental extubation (Analysis 7.1). Participants ventilated prone experienced a 10.5% event rate compared with 9.2% among those ventilated supine. The risk ratio was 1.09 (95% CI 0.85 to 1.39).

Tracheal tube obstruction

Three studies (Guerin 2004; Guerin 2013; Taccone 2009) of 1599 participants reported the complication of tracheal obstruction. These three studies strongly favoured the supine position, although moderate heterogeneity was noted, with I^2 statistic= 31% requiring use of a random-effects model for analysis (Analysis 7.1). The overall prevalence of tracheal obstruction for those ventilated prone was 15.9% compared with supine, which was 9.7%. The risk ratio was 1.78 (95% CI 1.22 to 2.60; P value = 0.003).

Pneumothorax

Four studies (Chan 2007; Fernandez 2008; Guerin 2013; Mancebo 2006) of 664 participants reported an event rate for pneumothoraces (Analysis 7.1), and one study (Guerin 2004) of 791 participants (and therefore not part of the quantitative meta-analysis) reported pneumothoraces per participant day. The four studies reported an overall event rate of 6.6% for participants ventilated prone and 5.4% for those ventilated supine, with a risk ratio of 1.16 (95% CI 0.65 to 2.08). The largest single study reported risk for pneumothorax per participant day of 0.38% for

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prone ventilated participants and 0.54% for supine ventilated participants, with an odds ratio of 0.71 (95% CI 0.40 to 1.24).

Arrhythmias

Three studies (Guerin 2013; Mancebo 2006; Voggenreiter 2005) of 642 participants reported on the prevalence of arrhythmias including bradyarrhythmias and cardiac arrest, noting a rate of 15.3% for those ventilated prone and 24.7% for those ventilated supine (Analysis 7.1). This analysis was dominated by one study (Guerin 2013). The risk ratio was 0.64 (95% CI 0.47 to 0.87). One other study (Guerin 2004) of 791 participants and 10,942 event days (and therefore not part of the quantitative meta-analysis) reported bradycardic episodes per participant day as well as cardiac arrests per participant day. For bradycardic episodes per participant day, the rate was 1.41% for prone ventilation and 1.39% for supine ventilation, with an odds ratio of 1.01 (95% CI 0.74 to 1.40). For cardiac arrest, the prevalence for prone ventilation was 1.51% per participant day and for supine 1.70% per participant day, with an odds ratio of 0.89 (95% CI 0.66 to 1.20).

Composite outcome of hypotension, arrhythmias and increased vasopressor use per participant day

This composite outcome was reported by one study (and therefore not part of the quantitative meta-analysis) of 342 participants and 5524 participant days (Taccone 2009). The reported rate of such cardiovascular compromise was 18% for participants ventilated prone and 12.4% for those ventilated supine, with a risk ratio of 1.45 (1.28 to 1.65; P value < 0.00001) favouring the supine position.

Quality of life

Only one study (Chiumello 2012) (and therefore not part of the quantitative meta-analysis) reported on quality of life for a small subset of 26 participants from five centres (187 participants) followed up from the Taccone 2009 study of 342 participants. The main quality of life metrics employed were the Short Form-36 (SF-36) questionnaire, which reported on eight items, and the Saint George's Respiratory Questionnaire (SGRQ), which reported on four items. For all domains in the SF-36 questionnaire, results were similar for all groups. For all four SGRQ items, the prone group performed better, but none of these results were statistically significant.

With regards to pulmonary function assessment with standard pulmonary function tests and quantitative evaluation of CT scans, 15 items were evaluated. Two results were statistically significant, and one was of borderline significance. These were PaO_2 (P value = 0.03) - reported as the PaO_2/FIO_2 quotient in the oxygenation section above; and over-aerated lung tissue on CT scan analysis of 12.5% of total lung weight for participants treated prone versus 5.3% for those treated supine (P value = 0.008). Mean results for well-aerated lung tissue between groups showed 64.0% for participants treated prone versus 70.2% for those treated supine (P value = 0.052).

Economic outcomes

None of the identified studies provided data on economic outcomes.

Planned subgroup analyses (SGA)

Analyses combining short- and longer-term mortality allow for one model (fixed-effect or random-effects) only per analysis. In two cases (Analysis 1.6; Analysis 1.10), short- and longer-term analyses required different models. Results presented in the text show actual result based on the correct model. All other analyses presented are correct.

Duration of daily ventilation in the prone position (< 16 hours/d vs ≥ 16 hours/d)

Mean daily application of prone ventilation for the nine included studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009; Voggenreiter 2005) was 16.3 hours (range 7 to 24 hours/d) given over a mean of 6.2 days (range 1 to 11.9 days). Mean total hours of prone ventilation for participants in each study ranged from 24 hours (Leal 1997) to 238 hours (Fernandez 2008), with a mean of 100 hours across included studies.

Two studies (Gattinoni 2001; Guerin 2004) of 1095 participants reported short-term mortality for participants ventilated less than 16 hours/d in the prone position (Analysis 1.2). Mortality was 37.3% for participants ventilated prone and 36.2% for those ventilated supine, yielding a risk ratio for mortality of 1.04 (95% CI 0.89 to 1.21). Three studies (Gattinoni 2001; Guerin 2004; Voggenreiter 2005) of 1135 participants reported on longer-term mortality for participants ventilated in the prone position for less than 16 hours per day. Mortality was 47.1% for participants ventilated prone and 45.9% for those ventilated supine, yielding a risk ratio for mortality of 1.03 (95% CI 0.92 to 1.17).

Six studies (Chan 2007; Fernandez 2008; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) of 1022 participants reported on short-term mortality for participants ventilated 16 or more hours per day, with moderate heterogeneity identified (I^2 statistic = 41%) (Analysis 1.3). Short-term mortality was 29.2% for participants ventilated prone and 40.5% for those ventilated supine, yielding a risk ratio of 0.73 (95% CI 0.58 to 0.93; P value = 0.01). Five studies (Chan 2007; Fernandez 2008; Guerin 2013; Mancebo 2006; Taccone 2009) of 1005 participants also reported longer-term mortality of participants ventilated prone for 16 or more hours per day. Longer-term mortality was 36.1% for those ventilated prone and 48.6% for those ventilated supine, with a risk ratio of 0.77 (95% CI 0.61 to 0.99; P value = 0.04).

The statistical test for subgroup differences for longer-term outcomes regarding daily duration of prone ventilation was significant (P value = 0.03; I^2 statistic = 78.0%), which provides stronger evidence for benefit of longer duration with the prone position (Analysis 2.1). The quality of the evidence as rated by GRADE was moderate (Summary of findings for the main comparison), with downgrading based on the potential for risk of bias.

Duration of supine ventilation before randomization (< 48 hours vs ≥ 48 hours)

Five studies (Fernandez 2008; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) of 1000 participants enrolled most participants within 48 hours of initiation of mechanical ventilation, allowing exploration of effects on short-term mortality (Analysis 1.4). Moderate heterogeneity was noted (I^2 statistic = 51%). Short-term

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mortality among prone participants was 29.0% compared with 40.6% among those in the supine group, with a risk ratio of 0.72 (95% CI 0.56 to 0.93; P value = 0.01). Five studies (Fernandez 2008; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005) of 1024 participants enrolled most of their participants up to 48 hours after initiation of mechanical ventilation with regards to longer-term mortality (Analysis 1.4). Moderate heterogeneity (I^2 statistic = 50%) was noted. Longer-term mortality among prone participants was 34.3% compared with 46.9% in participants randomly assigned to supine ventilation, with a risk ratio of 0.75 (95% CI 0.59 to 0.94; P value = 0.01).

Three studies (Chan 2007; Gattinoni 2001; Guerin 2004) of 1117 participants enrolled most participants more than 48 hours after initiation of mechanical ventilation (Analysis 1.5). Short-term mortality for prone participants was 37.7% compared with 36.2% in the supine group, with a risk ratio of 1.04 (95% CI 0.89 to 1.21). Three studies (Chan 2007; Gattinoni 2001; Guerin 2004) of 1116 participants enrolled participants after 48 hours or did not state enrolment time. For those ventilated prone, reported mortality was 48.6% compared with 47.2% for those ventilated supine. The overall risk ratio was 1.04 (95% CI 0.92 to 1.17).

The statistical test for subgroup differences for longer-term outcomes regarding timing of enrolment for prone ventilation was significant (P value = 0.01; I^2 statistic = 84.4%), and this provides stronger evidence for the benefit of longer duration with proning (Analysis 2.2). The quality of evidence as rated by GRADE was moderate (Summary of findings for the main comparison), with downgrading based on the potential for risk of bias.

Outcome according to severity (PaO_2/FIO_2 ratio; severity of illness score, e.g. Simplified Acute Physiology Score II (SAPS II); oxygenation index)

With regards to short-term outcomes, six studies (Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) of 744 participants explored the effects of prone position in a subset of participants with severe hypoxaemia - PaO_2/FIO_2 quotient < 150 mmHg (< 20.0 kPa) (Leal 1997); < 105 mmHg Guerin 2013); or < 100 mmHg (< 13.3 kPa) - and in four others based on reanalysis of original data (Gattinoni 2010; Sud 2010). For short-term mortality among participants with severe hypoxaemia (Analysis 1.6), adoption of prone ventilation was associated with 40.6% mortality in comparison with mortality of 50.1% for those ventilated supine, yielding a risk ratio of 0.80 (95% CI 0.68 to 0.93; P value = 0.003) when a fixed-effect model was used with I^2 statistic = 0. (The figure in the analysis presents results of the random-effects model, as longer-term outcomes required application of a random-effects model.) Twenty-eight-day mortality data (as opposed to short-term mortality) resulting from the combination of original studies and a review (Gattinoni 2010) showed near identical results, with a risk ratio of 0.80. For longer-term mortality, seven studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009) of 977 participants with severe hypoxaemia recorded mortality of 41.5% for participants ventilated prone and 54.7% for those ventilated supine, with a risk ratio of 0.77 (95% CI 0.65 to 0.92; P value = 0.003) when a random-effects model was used (Analysis 1.6). Moderate heterogeneity was detected (I^2 statistic = 39%). These results for short-term and longer-term mortality remained significant without inclusion of the most recent trial (Guerin 2013), which itself recorded highly significant results for short- and longer-term mortality (P value < 0.001 for both time periods in favour of prone positioning). The quality of the evidence as rated by GRADE was moderate (Summary of findings for the main comparison), with downgrading based on the potential for risk of bias.

For participants with less severe hypoxaemia, no apparent benefit was observed (Analysis 1.7). Short-term mortality from four trials (Gattinoni 2001; Guerin 2004; Mancebo 2006; Taccone 2009) of 1095 participants with milder hypoxaemia (PaO_2/FIO_2 ≥ 100 mmHg to 300 mmHg) failed to establish benefit of prone positioning, with a risk ratio of 1.03 (95% CI 0.87 to 1.21; I^2 statistic = 0). Although data from one other study (Guerin 2013) were available, this study included only participants with PaO_2/FIO_2 ≥ 105 mmHg to 150 mmHg and did not reflect the full spectrum of milder disease, as was evident in the other studies. Therefore, this study was excluded from the analysis. Data were also available from six studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Mancebo 2006; Taccone 2009) of 1108 participants undertaken to explore longer-term effects of the prone position applied in milder hypoxaemia (PaO_2/FIO_2 > 100 mmHg to 300 mmHg). The risk ratio for this group of participants was 1.06 (95% CI 0.93 to 1.21) and heterogeneity was negligible (I^2 statistic = 1%). For long-term outcomes with regards to severity of hypoxaemia, the statistical test for subgroup differences (Analysis 2.3) was significant (P value = 0.005; I^2 statistic = 85.7%).

Two studies (Gattinoni 2001; Mancebo 2006) provided sufficient data to allow exploration of the effects of physiological severity of illness on outcome, with data for one study derived from a journal comment (Sud 2008b). Heterogeneity between studies was considerable. For participants (327) with an SAPS II score of 49 or less, short-term mortality was 25.8% among those ventilated prone in comparison with 28.5% in those ventilated supine, yielding a risk ratio of 0.85 (95% CI 0.45 to 1.60; I^2 statistic = 69%) (Analysis 1.8). For participants (113) with greater severity of illness (SAPS II ≥ 50), short-term mortality among those ventilated prone was 34.7% and 56.8% for those ventilated supine, with a risk ratio of 0.60 (95% CI 0.25 to 1.40; I^2 statistic = 79%). Amalgamated data for two different time intervals (Gattinoni 2001 provided 10-day mortality data and Mancebo 2006 provided ICU mortality data) were not available for analysis of longer-term mortality.

Data regarding oxygenation index, most commonly reported in paediatric studies, were not available for analysis. (Oxygenation index was calculated as mean airway pressure × FIO_2 × 100/PaO_2 in mmHg and was expressed as a unit-less number.)

Tidal volume (6 to 8 mL/kg vs > 8.0 mL/kg of ideal body weight)

Three studies (Chan 2007; Guerin 2013; Taccone 2009) of 830 participants reported on the effects of ventilation with lower tidal volumes (mean of 6 to 8 mL/kg ideal body weight) on short-term mortality (Analysis 1.9). Mortality for the prone subgroup was 25.5% compared with 36.7% among those ventilated supine. The risk ratio was 0.72 (95% CI 0.43 to 1.20; P value = 0.2). Substantial heterogeneity was noted (I^2 statistic = 76%). Five studies (Chan 2007; Fernandez 2008; Guerin 2013; Taccone 2009; Voggenreiter 2005) of 910 participants reported on longer-term mortality among participants ventilated with low tidal volumes (mean 6 to 8 mL/kg ideal body weight). Mortality for those ventilated prone was 32.5% and for those ventilated supine 45.1%, with a risk ratio of 0.73 (95%

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CI 0.53 to 0.96; P value = 0.02). Heterogeneity was moderate (I^2 statistic = 43%).

Three studies (Gattinoni 2001; Guerin 2004; Mancebo 2006) of 1231 participants utilized high tidal volumes (mean > 8.0 mL/kg ideal body weight) and reported on short-term mortality (Analysis 1.10). Mortality for participants ventilated prone was 38.1% and for participants ventilated supine was 38.5%, with a risk ratio of 0.99 (95% CI 0.86 to 1.14; I^2 statistic = 38%; random-effects model). Those studies (Gattinoni 2001; Guerin 2004; Mancebo 2006) with 1231 participants also reported on longer-term mortality among participants ventilated with high tidal volumes. Mortality for those ventilated prone was 48.8% and for participants ventilated supine 48.5%, with a risk ratio of 1.01 (95% CI 0.9 to 1.13; I^2 statistic = 19%; fixed-effect model).

We categorized studies on the basis of mean tidal volumes (mL/kg) derived from ideal body weight (IBW) as provided by primary studies or imputed from actual body weight data. Two studies provided no measurements (Leal 1997; Voggenreiter 2005). The upper 95% confidence limit for tidal volumes was 7.3, 9.4, 9.8, 11.3, 14.6, 14.7 and 15.8 mL/kg IBW for the seven studies of Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006 and Taccone 2009. Notably, only one study (Guerin 2013) actually achieved the 6 to 8 mL/kg ideal body weight envelope in terms of the 95% CI approximating what is currently considered best clinical practice (Needham 2012).

A random-effects model used to test for subgroup differences between low and high tidal volume ventilation strategies yielded significant findings (P value = 0.04; I^2 statistic = 76.5%), strengthening evidence for the prone position in combination with lower tidal volumes (Analysis 2.4). The quality of evidence as rated by GRADE was moderate (Summary of findings for the main comparison), with downgrading based on the potential for risk of bias.

Analysis of studies of ALI and ARDS separate from other causes of acute severe hypoxaemic respiratory failure

Seven studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) were included in this subgroup analysis of 1326 participants ventilated for ARDS with regards to short-term mortality (Analysis 1.11). Data from Guerin's first study were not included, as inclusion criteria were broader than just ARDS participants (Guerin 2004). Mortality for those ventilated prone in these subgroups of ARDS participants was 34.0% compared with 42.6% for those ventilated supine. The risk ratio was 0.79 (95% CI 0.63 to 1.00; P value = 0.05). Heterogeneity was moderate (I^2 statistic = 57%). Eight studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005) were included in this subgroup analysis of 1758 participants ventilated for ARDS with regards to longer-term mortality. Ninety-day mortality for ARDS participants (PaO_2/FIO_2 quotient < 300 mmHg) from the first study of Guerin (Guerin 2004) became available through a recent meta-analysis (Sud 2014). Very minor adjustments were made to original data from another trial (Gattinoni 2001) on the basis of information obtained from this same meta-analysis. Mortality for those ventilated prone in these subgroups of ARDS participants was 41.3% compared with 48.3% for those ventilated supine. The risk ratio was 0.85 (95% CI 0.71 to 1.01; P value = 0.07), and heterogeneity was moderate (I^2 statistic = 56%). The quality of the evidence as rated by GRADE was moderate (Summary of findings for the main comparison), with downgrading based on the potential for risk of bias.

Pulmonary and extrapulmonary causes of ALI or ARDS

Data were insufficient to allow any analysis.

Use of meta-regression to explore heterogeneity between subgroups

Identified studies were insufficient to meet criteria for use of meta-regression techniques (Deeks 2011).

Sensitivity analysis based on potential bias or confounding

Removing studies on the basis of potential bias or confounding had little effects on most results. Excluding the studies of Guerin (Guerin 2004) on the basis of the high percentage of cross-over participants; of Voggenreiter (Voggenreiter 2005) because of the hugely disparate blood transfusion requirements between groups and differential use of muscle relaxants; and of Chan (Chan 2007) because only one assessment for risk of bias out of a total of seven was rated as "low" (Figure 2), produced a small shift in risk ratio for short-term mortality from 0.84 to 0.79 (95% CI 0.61 to 1.01), and from 0.87 to 0.82 (95% CI 0.65 to 1.04) for longer-term mortality.

DISCUSSION

Summary of main results

The main findings of this review are presented here.

Primary outcomes

Among all-comers entered into identified randomized controlled clinical trials, a statistically insignificant signal of benefit was seen for prone ventilation, with risk ratios of 0.84 and 0.86 for short-term and longer-term mortality. The last published trial (Guerin 2013) approximately halved mortality in its cohort of more severely hypoxaemic participants compared with other included studies, and changed heterogeneity as measured by the I^2 statistic from 0% to 60% or more for both primary outcomes. The risk ratio before publication and inclusion of this study was close to unity. This suggests that unselected participants with moderate to severe hypoxaemia requiring mechanical ventilation and given ventilation in the prone position may be too diffuse a target population for this intervention. When the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system was applied, evidence for benefit in unselected populations was rated low (Summary of findings for the main comparison), as the overall rating of quality of evidence was downgraded as a result of risk of bias and inconsistency (Guyatt 2008; Guyatt 2011a; Guyatt 2011c). Longer-term mortality would seem a more important patient-centred outcome when compared with short-term mortality for primary outcomes and for prespecified subgroup analyses of mortality (Hough 2012; Wang 2014; Williams 2008), and formal application of the GRADE approach was limited to primary outcomes and to selected subgroup outcomes for longer-term mortality.

One trial later reported a subset of 187 participants, for whom additional 12-month mortality data were reported (Chiumello 2012). This subset from five centres based in or near Milan,

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Italy, comprised more than 50% of the population of the original or primary trial (Taccone 2009). For this subset, no evidence showed benefit for prone ventilation in unselected participants with regards to 12-month mortality, as the risk ratio was slightly greater than unity, although findings were statistically insignificant.

With regards to heterogeneity, primary outcomes fell into the moderate heterogeneity category (Higgins 2003), and formal analysis was undertaken with a random-effects model, wherein the I^2 statistic exceeded 25%. In addition, recommended approaches for exploring heterogeneity through pre-specified subgroup analyses and for excluding studies in sensitivity analyses were undertaken. With only eight studies available for each of the two primary outcomes (short-term mortality - Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009; and longer-term mortality - Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005), we did not utilize meta-regression techniques, in accordance with best practice (Deeks 2011).

Secondary outcomes

Pneumonia

Pneumonia is an important complication, which definitely increases resource utilization and prolongs intensive care unit (ICU) and hospital length of stay with uncertain attributable mortality. Analysis of data from more than 1000 participants showed a trend towards a reduced rate of pneumonia only. The prevalence of pneumonia varied across studies, and to what extent this was driven by different patient populations (patient diversity) and criteria used to diagnose pneumonia (methodological diversity) is uncertain. In terms of this, diagnosis of ventilator-associated pneumonia is problematic, given the various criteria in clinical use (Klompas 2008; O'Brien 2011; Stevens 2014; Sud 2008) over the 15-year time span of these clinical trials.

Duration of mechanical ventilation

Duration of mechanical ventilation was reported in three studies of more than 800 participants (Fernandez 2008; Guerin 2004; Voggenreiter 2005). A small signal suggested benefit from prone positioning. However, the point estimate amounted to less than a half-day and cannot be considered a major patient-centred benefit. Such data are made complicated to interpret by differential patient mortality between groups, which will affect time data such as duration of mechanical ventilation and length of stay.

Length of stay (LOS)

Length of stay (LOS) data are difficult to interpret in that they are often skewed (Weissman 1997), and LOS will be influenced in diverse and opposite ways by the effectiveness of treatment. LOS may be reported as median and interquartile range (IQR), and sometimes as mean and standard deviation. The former data pose difficulties for meta-analysis, although they can be used if it is assumed that the median approximates the mean together with a statistical multiplication factor used to impute the standard deviation (Higgins 2011b). For skewed data, reporting of means and standard deviations may be misleading. It is recommended that both should be reported (Weissman 1997). Furthermore, effective treatment may reduce the LOS of participants already destined to survive but will lengthen the stay of those who would have died but have survived as a result of receiving the intervention. The overall effect will be determined by the balance of these two effects.

In this systematic review, mean and standard deviation were imputed for one study on the basis of non-parametric data (Taccone 2009). Point estimates for ICU LOS were similar with and without this study and favoured supine, with the mean difference in LOS between 1.34 and 1.37 days and not statistically significant. Only one study (Fernandez 2008) of 40 participants reported on hospital LOS; this again favoured supine ventilation, with the point estimate showing a difference of 5.8 days. Reduction in ICU LOS was not apparent with the use of prone ventilation in the four relevant studies (Fernandez 2008; Guerin 2004; Mancebo 2006; Taccone 2009). Data for hospital LOS were too sparse to allow meaningful comment.

Improved oxygenation

Improved oxygenation in participants ventilated prone was apparent at seven to 10 days in the outcome studies included in this systematic review. The mean difference in the PaO_2/FIO_2 quotient of 24.6 mmHg or 3.3 kPa is clinically meaningful and was statistically highly significant (P value < 0.00001). In a very small subset of participants (26) from the original Taccone trial (384 participants) examined at 12 months, residual benefit was not apparent, and a small but statistically significant benefit favoured supine-ventilated participants (Chiumello 2012). Thus oxygenation was substantially improved while participants were critically ill (Analysis 6.1), but robust evidence that this benefit is carried on to or beyond 12 months was not available.

We did not include the second study of Guerin (Guerin 2013) in the analyses, as formally mandated reduction in PEEP would negatively impact oxygenation and would confound such results.

Adverse effects

Studies show that pressure sores and tracheal tube obstruction were increased by mechanical ventilation provided in the prone position. Cardiac arrhythmias were reduced with use of the prone position. This was described in different ways by different studies and required separate analyses for the same complication, sometimes leading to inconsistent results. An important factor for interpretation is how vigorously these events were classified and sought within individual studies (Bent 2006; Ioannidis 2006).

- With regards to pressure sores, three studies (Chan 2007; Gattinoni 2001; Voggenreiter 2005) demonstrated a statistically significant effect of pressure sores per participant among those ventilated prone (P value = 0.02). Another single study, reporting in such a way that it could not be included in the meta-analysis, demonstrated the same trend but with borderline statistical significance (P value = 0.09). All four studies favoured the supine position with regards to development of pressure sores. This finding would be consistent with the area of tissue in contact with the bed during supine and prone ventilation and is biologically plausible.
- Tracheal tube displacement, which might be considered a natural consequence of moving patients from supine to prone position and back, showed differing results across studies, with moderate statistical heterogeneity. For example, the short-term (24-hour) study of Leal 1997 reported 50% tracheal tube displacement, whereas Chan 2007, which utilized at least 72

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hours of proning per participant, reported a zero rate of displacement. Overall the risk ratio was 1.09 and was statistically insignificant. However, a clear increase in risk of tracheal tube obstruction was evident. Such obstruction might result from increased inspissated secretions or from kinking of the tracheal tube in the face-down participant. The risk ratio for this complication was 1.78 and was statistically significant (P value = 0.003).

- Pneumothoraces were counted as events per participant in four studies (Chan 2007; Fernandez 2008; Guerin 2013; Mancebo 2006), and as events per participant day in one study (Guerin 2004). Three studies favoured the supine position (Chan 2007; Guerin 2013; Mancebo 2006), and two favoured the prone position (Fernandez 2008; Guerin 2004); evidence favouring one position or another is weak.
- With regards to arrhythmias or bradycardias, the most recent study (Guerin 2013) heavily influences overall findings. The point estimate was 0.64 (P value = 0.005) in favour of the prone position. A statistically insignificant trend from a single study (Guerin 2004) favoured the prone position with regards to cardiac arrests. However, Taccone 2009, when using the composite endpoint of "hypotension, arrhythmias or increased vasopressor requirements", strongly favoured the supine position (P value = 0.001) (Glantz 2005).
- Ocular complications are described among patients undergoing undergoing general anaesthesia, for therapeutic purposes, with prone positioning an associated risk factor, and the incidence of perioperative visual loss ranges between 0.028% and 1.3% (Uribe 2012) in this setting. Permanent blindness can result from ischaemic optic neuropathy or from central artery occlusion, and the zero numerator from this systematic review of 1107 prone participants still indicates a 95% confidence interval of 0 to 0.27% for the incidence of such events (Hanley 1983). Clinicians should remain vigilant for ocular complications, given the potentially important long-term consequences; a recent abstract has highlighted one such case (Ayoubieh 2014).

It is difficult to gauge the relevance of some of the reported findings in terms of the methodological rigour of their detection (Ioannidis 2006) and their clinical importance.

Quality of life (QOL)

With regards to quality of life (QOL), only one study of 26 participants has addressed this issue - Chiumello 2012. No clear benefit was seen in this very small study, which encompassed a subgroup of participants originating in the Taccone 2009 trial. Firm conclusions with such a small number of participants would seem inappropriate. More evidence is required.

Intensive care patients comprise a diverse population of individuals admitted from all different hospital specialities, and the aetiology of acute respiratory distress syndrome (ARDS) is similarly diverse (Walkey 2012). The more inclusive umbrella of hypoxaemic respiratory failure is even more disparate. This participant heterogeneity reduces the power of studies and increases the sample size required to avoid type II statistical error (Lipsey 1990). The power of studies to detect differences in outcome is hindered by participants who have crossed over to the opposite treatment. Cross-overs occurred in several studies to a greater or lesser extent (34% of participants in one study, Guerin 2004). This may be important for this systematic review, for which participant numbers available for exploratory analyses are only modest to moderate. Given the importance of optimum treatment of severely hypoxaemic patients in ICUs, it is disappointing that at least three studies had to be terminated prematurely because of poor participant accrual (Fernandez 2008; Gattinoni 2001; Mancebo 2006). The almost complete absence of long-term survival data (12 months and beyond), physiological function data, QOL life data and economic data is notable and is limiting with regards to overall evaluation of the benefits (or otherwise) of prone positioning as an adjunct to conventional mechanical ventilation. Such data are likely to be more relevant to patients, their families and society, when compared with short-term mortality outcomes alone (Herridge 2011; Hough 2012; Wang 2014).

Subgroup analyses

Given clinical diversity in terms of diagnoses and severity of illness (hypoxaemia), as well as methodological diversity, which has contributed to substantial statistical heterogeneity, pre-specified exploration of subgroups was warranted, and data will be of interest to stakeholders. Important issues associated with subgroup analysis include reduced statistical power, increasing type II statistical error; multiple statistical testing, increasing type I error and ecological fallacy in study-level meta-analyses. The multiple subgroup analyses reported below should be viewed in this light (Lagakos 2006; Oxman 1992; Reade 2008). Subgroup analyses are presented for short-term (10 to 30 days) and longer-term mortality (31 to 180 days, or hospital mortality). As mentioned earlier, longer-term mortality would seem more important than short-term mortality from the patient perspective, given reduced longer-term survival and the ongoing burden of disease following acute lung injury and intensive care stay (Herridge 2011; Hough 2012; Iwashyna 2010; Wang 2014; Williams 2008). Five subgroups are included in the Summary of findings for the main comparison, and all subgroup analyses were downgraded on the basis of potential for important risk of bias. Downgrading of evidence as a result of imprecision was considered on the basis of Figure 5 and Table 1 of Guyatt and colleagues (Guyatt 2011b), both of which base achievement of optimal information size (OIS) on sample size or number of events. Four of the subgroup analyses of longer-term mortality (Analysis 1.3; Analysis 1.4; Analysis 1.6; Analysis 1.11) clearly met suggested requirements for OIS, with the number of events (deaths) in the subgroup analyses ranging from 411 to 736. For the remaining analysis (Analysis 1.9) exploring the subset of participants ventilated with lower tidal volumes (Summary of findings for the main comparison), events were fewer, at 353. Nevertheless, we also judged the OIS to have been met by taking into consideration the control event rate and the actual relative risk reduction in this subgroup. Although all subgroup analyses demonstrated substantial heterogeneity, as indexed by I^2 statistical methods, further downgrading on the basis of inconsistency for these analyses was considered but not implemented, also in keeping with the approach recommended by Guyatt and colleagues (Guyatt 2011c).

Duration of prone ventilation

First, the duration or "dose" of prone ventilation might have an impact on outcomes, and we examined the effects of short periods and longer periods of prone ventilation per day. Short periods of ventilation in the prone position appeared to confer no benefit for participants with a risk ratio very close to unity. Periods of prone ventilation for 16 or more hours per day yielded point

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estimates of 0.73 and 0.75, which were statistically significant for both short-term (P value = 0.01) and longer-term mortality (P value = 0.04). We rated the quality of evidence as moderate using the GRADE structure (Summary of findings for the main comparison). We calculated dose of prone ventilation (with a two-hour change in cutoff) as per our published protocol (Bloomfield 2009). Other methods not employed in this review might also be considered. Total dosage of proning might be equally valid and might produce different results. For example, the most recent trial (Guerin 2013), despite proning for 17 hours per day, applied it for only four days (68 hours), and in terms of total hours prone for participants ranks as the fourth shortest across the nine included trials (Characteristics of included studies), after Leal 1997, Gattinoni 2001 and Guerin 2004. Two of the studies excluded from our review but not from others (Characteristics of excluded studies) applied prone ventilation for a single episode of 12 hours (Demory 2007; Papazian 2005), and two other excluded studies applied proning over six days, for a total of 24 hours only (Beuret 2002; Watanabe 2002).

Timing of intervention

We investigated whether early intervention offered an advantage as a strategy with the potential to ameliorate lung injury, as adoption later in the illness might limit benefit. Short-term mortality and longer-term mortality analyses of available data showed a risk ratio close to unity for three studies (Chan 2007; Gattinoni 2001; Guerin 2004), which enrolled more than 1000 participants after 48 hours. Participants enrolled earlier in five other studies (short-term mortality - Fernandez 2008; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009; longer-term mortality - Fernandez 2008; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005) demonstrated a large effect favouring prone ventilation, with risk ratios of 0.72 and 0.75, which were statistically significant (P values = 0.01 and 0.01) for short-term and longer-term mortality for a participant sample of 1000 or more. The quality of the evidence was rated as moderate when the GRADE structure was applied (Summary of findings for the main comparison).

Severity of injury

It has been postulated that prone positioning might benefit participants with the most severe lung insult, and data are available from original trials and from further published analyses of the original trials (Gattinoni 2010; Sud 2010). With all trials included that provided data for participants with the most severe hypoxaemia, a large and statistically significant apparent benefit can be seen, with point estimates of 0.80 and 0.74 for short- and longer-term mortality (P values = 0.003 and 0.003). The quality of the evidence was rated as moderate according to the GRADE structure (Summary of findings for the main comparison). Removing data for two additional studies (Gattinoni 2001; Guerin 2004) provided by Sud et al, in which the precise timing of mortality assessment was not specified (Sud 2010), did not change the outcome of this subgroup analysis. Prone ventilation of participants with milder hypoxaemia appeared to confer no benefit, with risk ratios of 1.03 and 1.06 for short- and longer-term mortality. However, the second study of Guerin et al (Guerin 2013) was influential in the overall analysis: Overall short-term mortality in control groups of the other studies that reported participants with severe hypoxaemia was 58.5%, with mortality of 49.6% among participants treated prone. These rates differ substantially from those of Guerin et al (Guerin 2013), who reported percentage rates of 33.9 and 20.7 with absolute risk reductions of 8.9% for all other studies and 13.2% for Guerin et al. Of particular note is the much lower control mortality observed in the study of Guerin et al compared with other studies. This might be explained by the more rigid application of available evidence-based practices not fully utilized by earlier investigators (ARDS Network 2000), as well as by more recent evidence (Papazian 2010), which would not have been known or applied in earlier studies. However, this does not fully explain the apparent differences in absolute risk reduction resulting from application of prone positioning.

With regards to overall severity of acute illness (SAPS II scoring system), heterogeneity between studies was considerable. Total numbers of participants studied and actual events (deaths) were low, generating unacceptable imprecision (Guyatt 2011b). This further reduces the relevance and credibility of this analysis. Additionally, two different short-term outcomes were reported and amalgamated (Gattinoni 2001;.Mancebo 2006; Alsaghir 2008; Sud 2008b): Gattinoni 2001 provided 10-day mortality data for analysis (70 deaths), whereas Mancebo 2006 provided ICU mortality data. ICU mortality data from Gattinoni 2001 would have provided another 80 deaths for analysis, and the comment in this paper that "These differences in [10 day] mortality rate did not persist after discharge from the intensive care unit (data not shown)" suggests limited relevance of these published data. Use of a random-effects model to combine data demonstrated lower mortality for participants ventilated in the prone position for both lower and higher severity of illness, but with wide confidence intervals. Both studies were conducted during the high tidal volume ventilation era, making their results even less relevant in the modern mechanical ventilation era. For multiple reasons, as listed above, available data do not support severity of acute illness (SAPS II) as a basis for selection of participants for application of prone ventilation.

Ventilation strategy

As mentioned in the previous section, before publication of the first ARDS Network study (ARDS Network 2000), high tidal volume ventilation was in widespread use, but since low tidal volume ventilation has become the standard of care in clinical trials, it is increasingly used in clinical practice (ARDS Network 2000; Needham 2012; Petrucci 2007). Studies conducted before adoption of this standard may be carried out differently and may be less relevant to current practice (Verbrugge 2007). For studies using higher tidal volume ventilation, both short-term and longer-term risk ratios for mortality were close to unity. All four studies (Gattinoni 2001; Guerin 2004; Leal 1997; Mancebo 2006) totalling 1200 participants commenced recruitment of participants before the ARDS Network study was published (ARDS Network 2000). Slightly smaller numbers of participants (830 to 911) from identified trials were available for analysis of low tidal volume strategies. All of these trials except the most recent (Guerin 2013) did not achieve tidal volumes of 6 mL/kg of ideal body weight, and low tidal volumes were considered to be 6 to 8 mL/kg of ideal body weight for pragmatic reasons. These showed a risk ratio in favour of prone ventilation for both short-term (0.72) and longer-term mortality (0.73), which was statistically significant for longer-term mortality only (P value = 0.02). For longer-term mortality, this analysis also utilized the Voggenreiter 2005 study, which, although initiated before publication of the ARDS Network study, employed a low tidal volume lung-protective strategy. The quality of the evidence was rated as moderate according to the GRADE structure (Summary of findings for the main comparison). Analysis of more than 1200

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participants ventilated with higher tidal volumes demonstrated modest or little benefit, with a risk ratio of 0.97 for longer-term mortality. As use of higher tidal volumes is no longer recommended because of the propensity of this approach to cause ventilator-induced lung injury (Slutsky 2013), some may consider these older trials that pre-date lung-protective ventilation to have very limited relevance to current clinical practice. Notably, only the most recent study (Guerin 2013) truly employed an evidence-based low tidal volume lung-protective ventilation strategy (ARDS Network 2000), which is now considered a standard of care by many (Needham 2012). Guerin (Guerin 2013) reported a mean tidal volume of 6.1 mL/kg ideal body weight (95% CI 4.9 to 7.3). For all other studies, the 95% CI breached the 8 mL/kg ideal body weight upper limit for "lung-protective ventilation" (Characteristics of included studies), and a substantial proportion of participants in studies identified as having received "lung-protective ventilation" will not have done so if reported data were normally distributed.

Aetiology of hypoxaemia

Many aetiologies of hypoxaemia have been identified in ICU populations. Some involve specific treatments and may be effectively and rapidly reversible with non-ventilatory treatments such as diuretics or haemofiltration for fluid overload and pulmonary oedema. A major group of conditions collectively labelled as acute respiratory distress syndrome (ARDS) (Walkey 2012) are of particular interest to intensivists and warrant separate exploration. Acute lung injury, recently re-termed 'mild ARDS' (ARDS definition workforce 2012), is a less severe form of ARDS, is less threatening to life and is less of an immediate concern for intensive care physicians compared with ARDS (Walkey 2012; ARDS definition workforce 2012). Only one study of 791 participants included a large proportion of participants with conditions other than ARDS or ALI (Guerin 2004). Outcomes of participants from this clinical trial (Guerin 2004) became available in a recent systematic review (Sud 2014), providing more than 1700 participants for analysis of longer-term outcomes, but these results changed little overall. The subgroup of participants with predominantly ARDS or ALI (mild ARDS) demonstrated risk ratios of 0.79 and 0.82 (P values = 0.05 and 0.07). This compares with analyses of all-comers with hypoxaemia who had risk ratios of 0.84 and 0.86 for short- and longer-term mortality. The quality of the evidence was rated as moderate in accordance with the GRADE structure (Summary of findings for the main comparison).

The first study conducted by Guerin et al reported a high rate (32%) of cross-over (Guerin 2004; Sud 2008), and removal of this trial on the basis of inclusion of patients without ARDS serves as a sensitivity analysis for excessive cross-overs - that is, removal from the above analysis also results in exclusion of the only study with a very large cross-over population.

Overall completeness and applicability of evidence

From primary outcomes analyses of all available studies comes only weak evidence of benefit for application of prone ventilation to all-comers with hypoxaemic failure who met trial entry criteria in the included studies. Evidence suggests that targeted application to certain subgroups would be appropriate.

The most recently published study (Guerin 2013) has had a large impact on overall results and interpretation of the impact of prone ventilation on primary and secondary outcomes of that intervention. This study investigated the effectiveness of prone ventilation in what would be a population subset of most of the other cited studies (more severe hypoxaemia as a fundamental trial entry criterion). In the study of Guerin et al (Guerin 2013), mortality was approximately halved, which is extraordinary for any medical intervention. This study had a large impact on overall effect size and on assessment of heterogeneity in this systematic review.

Additionally, many studies (Gattinoni 2001; Guerin 2004; Leal 1997; Mancebo 2006) were conducted in an era before lung-protective ventilation became a standard of practice, thus reducing external validity; results of those studies are likely to be very limited in relation to current practice. Restriction to studies that employed a more lung-protective strategy with means of 6 to 8 mL/kg tidal volume did result in a risk ratio point estimate of 0.71 for longer-term mortality, which was statistically significant (P value = 0.05).

One subgroup analysis that requires specific mention is the analysis of mortality of patients with severe hypoxaemia. For short-term mortality in six studies of 744 participants (Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009), the risk ratio was 0.80 (95% CI 0.68 to 0.93; P value = 0.003) in favour of prone positioning with a fixed-effect model. For longer-term mortality, seven studies of 977 participants (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009) also demonstrated a risk ratio in favour of prone positioning of 0.77 (95% CI 0.70 to 0.95; P value = 0.003) by using a random-effects model. Although the quality of the evidence was rated as moderate according to the GRADE structure (Summary of findings for the main comparison), findings appear consistent in that the most recent trial (Guerin 2013), which focuses on participants with more severe hypoxaemia, on its own has shown a remarkable survival advantage for participants. This subgroup meta-analysis with the study included is highly statistically significant, and the subgroup meta-analysis remains significant when this recent study is removed from the analysis. The subgroup exploration fully supports the conclusions of the most recent randomized controlled trial (Guerin 2013) and adds support to use of prone position ventilation in this specific patient population.

This systematic review found no important signal of benefit among participants recruited after 48 hours upon meeting entry criteria and ventilated prone for less than 16 hours per day, nor among those ventilated with higher tidal volumes or among those with milder hypoxaemia. An earlier systematic review (Sud 2010) also suggested no benefit for patients with moderate hypoxaemia only.

Quality of the evidence

With regards to the primary outcome of mortality, eight studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) were available for short-term mortality, and eight studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005) were available for longer-term mortality. Each analysis included data from more than 2100 participants, and internal validity of results must be considered good in that regard. Clinical diversity and methodological diversity (for some outcomes at least) may have contributed to statistical heterogeneity as assessed by the Higgins (I^2 statistical) method.

The trials were not triple-blind, and some bias would seem inevitable. We rated all studies to be at risk of bias in at

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least one domain (performance bias): All primary studies had at least one risk, as it would be difficult to blind participants and carers from their treatment allocation (face-up or face-down). Although actual assessment of alive or dead could not be affected (Guyatt 2011a), end-of-life practices are ubiquitous and poorly standardized clinically, and were not standardized in the included trials. The decision to continue with active management for a patient or to withdraw treatment, or to move to non-escalation of treatment (Morgan 2014; Turnbull 2014) or other differential use of co-interventions for a participant, could be influenced by personal views. It is our assessment that some level of bias with regards to patient management is highly probable in all studies. Centres were not chosen at random, but rather by interest in this topic: An early study (Gattinoni 2001) was terminated "largely [because of] an increasing unwillingness among caregivers to forgo the use of prone positioning". Another study (Guerin 2013) stated, "Patients were recruited from 26 ICUs in France and 1 in Spain, all of which have used prone positioning in daily practice for more than 5 years". Unblinded trials are associated with exaggerated estimates of effect (Forbes 2013; Karanicolas 2010; Psaty 2010), and, although outcomes such as death are usually considered as relatively immune to bias, we believe this is not the case in intensive care, where mortality is high over a short time frame and death often is not directly related to hypoxaemia (Stapleton 2005; Turnbull 2014).

The GRADE assessment of quality of evidence for the primary outcomes of this systematic review was rated weak on the basis of bias (as discussed above) (Guyatt 2011a) and inconsistency (Guyatt 2011c). The Cochrane risk of bias assessment indicated that one trial had three different risks (Chan 2007) and two primary trials had two different risks (Guerin 2004; Voggenreiter 2005). These trials were subjected to a sensitivity analysis.

A small post hoc subgroup of 187 participants from one study (Chiumello 2012) allowed analysis of results at 12 months, which showed no signal of benefit for the prone position and so was inconsistent with the primary outcome measures. The quality of evidence for secondary outcomes and subgroup analyses varied in terms of numbers of participants available for analysis (113 to 1350) and quality of measurement, aspects of which have been mentioned in the secondary outcomes and subgroup analysis sections of the Discussion. Subgroups may not be independent, and this underscores the need to consider most as hypothesis-generating only in this study-level meta-analysis (e.g. the ARDS subgroup will likely also have worse hypoxaemia).

Removal of the Voggenreiter study (Voggenreiter 2005) from our meta-analysis as part of a sensitivity analysis, which did include a higher proportion of participants with acute lung injury (mild ARDS) and yielded a threefold higher rate of transfusion in the supine group as well as increased usage of neuromuscular blockers among participants treated prone, made little difference to this analysis. Also with regards to change in trial findings over time, the discrepancy between study initiation or completion and study publication was not constant. The time lag between study start (a surrogate of final trial protocol) and publication of results varied between five and eight years for published studies in this review. Time lag from study completion to publication varied from one to four years. Publication date may not be of greatest relevance for tagging studies with regards to the start of the lung-protective ventilation era and may lead to incorrect data interpretation. The study of Voggenreiter 2005, although commenced in 1999 and completed in 2001, actually used lung-protective ventilation before the influential ARDS Network study was published (ARDS Network 2000).

Potential biases in the review process

We believe that the likelihood of bias in the review process of evaluated material is low. Processes used to identify relevant studies included in this review have been supplemented by several high-quality systematic reviews, which also have involved nearly all of the key trialists. Therefore, it is likely that all relevant studies up to January 2014 were identified. Adherence to most prespecified study inclusion and exclusion criteria in the protocol stage was maintained in the review stage. The cutoff in one subgroup analysis (long-duration prone positioning) was changed by two hours from 18 hours per day to 16 hours per day post hoc in an effort to allocate and analyse the last published study (Guerin 2013) in the most biologically plausible manner consistent with the original protocol. Ecological fallacy or bias cannot be excluded in a study-level systematic review of participant subgroups (Porta 2008; Reade 2008).

We reran searches of CENTRAL, MEDLINE, EMBASE, CINAHL and LILACS in June 2015. We found 208 citations and added five new studies of potential interest to the list of Studies awaiting classification; we will incorporate these into formal review findings during the review update. One study (Zhou 2014) could provide new data for one of the primary outcomes (short-term mortality) of this systematic review. Two others (Ayzac 2014; Girard 2014) may contribute to analysis of secondary outcomes. In addition, new information may become available from two new systematic reviews (Hu 2014; Park 2015) on this topic.

Agreements and disagreements with other studies or reviews

At least 12 systematic reviews of prone ventilation have been published and considered in this review (Abroug 2008; Abroug 2011; Alsaghir 2008; Beitler 2014; Curley 1999; Gattinoni 2010; Kopterides 2009; Lee 2014; Sud 2008; Sud 2010; Sud 2014 Tiruvoipati 2008). Two additional studies found in our most recent search await evaluation (Hu 2014; Park 2015). None of the 12 appear to have published protocols pre-specifying their approach to data collection, management and analysis, which, since 2009, is a preferred option according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher 2009), with the possible exception of Sud 2014. Three systematic reviews (Gattinoni 2010; Sud 2010; Sud 2014) are extensively represented by authors of primary studies: In the systematic reviews of Sud et al (Sud 2010; Sud 2014), 13 of 17 listed review authors represent 10 of the 13 primary studies with mortality data, and in the systematic review of Gattinoni (Gattinoni 2010), five of six review authors represent the four primary studies included in those analyses.

Earlier systematic reviews (Abroug 2008; Alsaghir 2008; Curley 1999; Gattinoni 2010; Kopterides 2009; Sud 2008; Tiruvoipati 2008) did not include the two most recent trials (Guerin 2013; Taccone 2009) and are less relevant in terms of both current clinical practice and volume of appropriate data for analysis. Inclusion criteria have differed between reviews, and those with larger numbers of studies have not included exactly the same studies for analyses, even

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analyses carried out by the same group (Figure 5). For example, Abroug et al included the study of Curley 2005 in one meta-analysis (Abroug 2008) but not in their updated review (Abroug 2011). In this regard, two of the most recent reviews (Beitler 2014; Lee 2014) identified different numbers of studies for analysis: One (Beitler 2014) identified seven primary studies only and split one study into two to achieve eight data sets for their subgroup meta-analysis; the other (Lee 2014) identified 11 studies for inclusion in their analyses. Two of the analyses of Sud et al included 10 of 13 primary studies with mortality data (Sud 2010; Sud 2014), but review authors excluded three studies from their original systematic review (Sud 2008). In their most recent review, the review authors state, "Reviewers were in total agreement about the included studies"; however, all were authors of 10 of 11 of the included primary studies (Sud 2014).

Our systematic review specified at the protocol stage which studies would be included and which excluded; this has resulted in fewer studies for analysis compared with some of the reviews mentioned above (Bloomfield 2009). In particular, our review consisted of adult participants receiving conventional mechanical ventilation as treatment for hypoxaemia. Thus trials that studied children, prevention and non-conventional modes of ventilation were not considered for inclusion, and this largely accounts for the differences in numbers of participants studied in primary, secondary and subgroup analyses. Different studies have also provided different analyses. For example, in this systematic review, mortality was partitioned into short-term mortality, longer-term mortality and post hoc to 12-month mortality. Other reviews have aggregated the latest available data for mortality and have not split data into short-term and longer-term categories (Sud 2010). This has resulted in the advantages of increasing numbers of studies and participants available for analysis but obscures where any advantages for participants lie: Longer-term mortality may be of greater relevance to participants than short-term-mortality if "short-term" still equates to being on a ventilator, or still requiring ICU care. Nevertheless, this systematic review is in agreement with most other systematic reviews on this topic - that analysis of all studies fails to demonstrate unequivocal benefit for all participants with acute respiratory failure in terms of short- or longer-term mortality. It also is consistent with all reviews in finding that oxygenation is improved and pressure sores are increased (Sud 2010). This systematic review (Sud 2010) used data provided by the original investigators in many of the original trials and included many as co-review authors: Their report provided data (from last follow-up) on participants with severe hypoxaemia and moderate (or less severe) hypoxaemia. These data indicate that participants with moderate hypoxaemia only did not appear to benefit from prone ventilation, with a risk ratio 1.07 (95% CI 0.93 to 1.22; P value = 0.36) in favour of supine ventilation, which is consistent with the risk ratio of 1.06 obtained in our analysis.

One recently published systematic review (Abroug 2011) reached some conclusions that differed from the findings of our review. These review authors concluded that no increase occurs in airway complications related to the prone position. However, we found an increase in airway obstruction, as did Sud et al (Sud 2010), and clinicians should be aware of this potentially serious problem. In this regard, we found a risk ratio of 1.78 in favour of the supine position (P value = 0.003) when using a random-effects model for analysis. Analysing data from four studies only, Sud et al observed a statistically significant mortality benefit in a subgroup of studies enrolling ARDS participants only. They excluded the study of Gattinoni (Gattinoni 2001), although more than 94% of participants in that study met ARDS criteria. Only with publication of the most recent study (Guerin 2013) could we identify any signal of support, and this study included only participants with more severe ARDS. Even with inclusion of this study, statistical significance was not achieved for longer-term mortality in our analysis. Early systematic reviews (Abroug 2008; Alsaghir 2008; Kopterides 2009; Sud 2008; Tiruvoipati 2008) generally considered the totality of evidence for proning, but more recent aggregate-level systematic reviews (Abroug 2011; Beitler 2014; Sud 2010; Sud 2014) have focused on particular subgroups of patients and therefore are potentially subject to the problem of ecological fallacy.

We have evaluated three recent systematic reviews (Beitler 2014; Lee 2014; Sud 2014), which include the most recent clinical trial of Guerin and colleagues (Guerin 2013).

One review (Lee 2014) focusing on ARDS included studies that we specifically excluded (Beuret 2002; Demory 2007; Papazian 2005) for reasons listed in the Characteristics of excluded studies section. Inclusion of these studies reduced statistical heterogeneity but increased clinical diversity in the meta-analysis (Bloomfield 2014). The former effect resulted in a statistically significant result for their primary analysis. We maintain the view that inclusion of these three primary studies is not justified on scientific grounds. Our published protocol specifically excluded such studies a priori. The immense influence of the PROSEVA study (Guerin 2013) was not highlighted. Review authors also rated the risk of bias from lack of blinding of participants and personnel as low, in contrast to our rating of such bias as discussed earlier. Further, they excluded Gattinoni et al (Gattinoni 2001) from their ARDS analysis, although more than 94% of participants in that study met ARDS criteria (Bloomfield 2014). This meta-analysis has drawn criticism from other workers similar to the criticisms described above (Iftikhar 2015).

The second systematic review (Beitler 2014), which focused on ARDS in the low tidal volume era, did not include the small study of Chan (Chan 2007), listing it as an observational study without a clearly defined control group, nor that of Leal (Leal 1997). This review explored reasons for heterogeneity but did not address the consistent and most important determinant of heterogeneity in this regard - results from the PROSEVA study of Guerin et al (Guerin 2013). Review authors split the data from one trial (Taccone 2009) into two groups for their analysis, which we consider methodologically problematic. In this last regard, application of mechanical ventilation to more severely ill participants will almost inevitably lead to reduced mechanical ventilation tidal volumes (which was their justification for splitting one trial into two), as clinicians strive to reduce mean and peak ventilatory pressures, even though the two subgroups form one study sharing a single protocol over one study epoch. Their exploration of heterogeneity is puzzling in that effects of the PROSEVA trial (Guerin 2013) are not discussed at all.

Sud and colleagues (Sud 2014) have updated their original meta-analysis and have adopted a restrictive approach with regards to study selection for their primary analysis focused on ARDS. This review identified 11 studies, of which only six were used for the primary analysis. Thirteen of the 17 authors of this review contributed to 10 of the original studies, and they selected 11 for inclusion in their study-level meta-analysis. The primary analysis was restricted to a subset of studies describing participants with

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a diagnosis of ARDS and was further restricted to those receiving low tidal volume ventilation. Review authors included studies specifically excluded in this review (Beuret 2002; Curley 2005; Watanabe 2002) for reasons already described (Characteristics of excluded studies). Only one was used in the primary analysis (Curley 2005), which studied a paediatric population with a median age of two years. Review authors rated the quality of findings of their systematic review as high according to the GRADE structure in comparison with our assessment of low quality for our primary analyses and moderate quality for our main subgroup analyses (Summary of findings for the main comparison). A finding of low heterogeneity was emphasized, but no emphasis was placed on the substantial increase since the previous review (Sud 2010), most obviously resulting from inclusion of the most recent trial (Guerin 2013). The classification of heterogeneity is highly subjective, and a variety of ranges are suggested (Deeks 2011; Hatala 2005; Higgins 2003) for low, moderate and high heterogeneity. We used a more conservative approach and would have rated most of these analyses as demonstrating moderate heterogeneity. Likewise, the GRADE approach to assessment of the quality of evidence requires subjective judgement. We considered the risk of bias to be high, as discussed earlier. The inconsistency and increased heterogeneity of results before and after inclusion of the most recent trial (Guerin 2013) could have led to further downgrading of the quality of evidence for this subgroup analysis of participants with an ARDS diagnosis. In this regard, analyses performed before publication of this trial (Guerin 2013) and those that did not include it (nine of 11 analyses) yielded an I^2 statistic of 0% for short-term mortality. For longer-term mortality, nine of 11 studies also had an I^2 statistic = 0, and 10 of 11 had an I^2 statistic less than 25%. In contrast, with inclusion of the trial for short-term mortality, only one of six analyses revealed an I^2 statistic = 0 or less than 25%, and for longer-term mortality, zero analyses of six had an I^2 statistic = 0% or less than 25% (i.e. 19 of 22 analyses had zero or low heterogeneity without inclusion of data from Guerin 2013, in contrast to one of 12 analyses with inclusion of these data). With regards to statistical significance, despite increased heterogeneity and increased use of the random-effects model, the pattern was opposite: A P value of 0.05 or less was observed in two of the 22 analyses that did not include this influential study but in eight of 12 analyses that included it. The substantial impact of this trial is also apparent upon visual inspection of forest plots of mortality.

Our subgroup results agree in part with the main findings of Sud (Sud 2014), in that longer-term mortality appears reduced among participants receiving lower tidal volume ventilation (RR 0.73, 95% CI 0.55 to 0.96) and in severely hypoxaemic participants (RR 0.77, 95% CI 0.65 to 0.92), but results for participants with ARDS are only borderline in the analysis (RR 0.85, 95% CI 0.71 to 1.01). All three are only subgroup analyses of the greater body of evidence and in our view show moderate quality when assessed by the GRADE structure.

AUTHORS' CONCLUSIONS

Implications for practice

The intervention of prone positioning would involve very low cost with adequate staffing (or equipment) to safely turn patients from the supine to the prone position and back again, as required. If the intervention was effective with regards to patient-centred outcomes, this would almost certainly be translated into an intervention that was also cost-effective, provided that complications for patients and long-term injuries to staff from additional lifting of patients did not occur. Cost-effectiveness data and modelling or other economic data are currently not available.

Results of this systematic review do not provide strong support for use in all patients with hypoxaemic respiratory failure who are intubated and mechanically ventilated in intensive care: Although the risk ratio for short-term mortality and longer-term mortality with inclusion of the last published study provided a signal for benefit, evidence was weak for all participants with acute respiratory failure (Summary of findings for the main comparison). Indeed, post hoc analysis of a small subset of 187 participants examined at 12 months (Chiumello 2012) actually favoured supine ventilation for these participants but with wide confidence intervals.

Oxygenation improvement persisted after adoption of the prone position seven to 10 days after enrolment, but many studies have shown that improvement in oxygenation (e.g. with use of nitric oxide) is not a reliable surrogate for improved patient-centred outcomes (Adhikari 2007; Diaz 2010). This again appears to the case for the primary analyses of this systematic review of prone ventilation.

Complications were increased for pressure sores and for airway and cardiovascular events, and, although these did not translate into excessive mortality, clinicians need to be aware of these issues. A widely varying rate was reported for some of these complications across studies, reflecting perhaps that "low priority data" were provided by these studies (Ioannidis 2006), or that better implementation of preventative measures in some studies led to reduced complication rates.

Subgroup exploratory analyses, which are widely utilized in published studies and in this systematic review, must be treated with caution: Risks of type I and type II statistical errors are increased through reduced statistical power derived from decreased participant numbers and increased numbers of hypotheses tested and by risks of ecological fallacy associated with aggregate-level meta-analyses (Lagakos 2006; Oxman 1992; Reade 2008). Thus subgroup analyses must be interpreted with these weaknesses in mind. Analyses of subgroups from this systematic review revealed subgroups in which prone ventilation appeared to have no benefit, with a risk ratio of close to unity; subgroups with point estimates suggestive of benefit but with wide confidence intervals; and subgroups for which the point estimate was both suggestive of benefit and statistically significant.

- In particular, point estimates close to unity for prone ventilation of short daily duration, later application of prone ventilation after onset of hypoxaemia, milder hypoxaemia and ventilation with > 8 mL/kg ideal body weight indicated that prone positioning in these circumstances would be unlikely to provide benefit.
- In contrast, ventilation prone for 16 or more hours per day, early intervention with prone positioning after entry criteria were met and presentation of severe hypoxaemia point estimates suggest that prone positioning might be beneficial in these circumstances. Point estimates for risk ratio ranged from 0.72 to 0.80 in favour of prone ventilation. In the absence of alternative evidence, it is recommended that prone position should be actively considered for such patients. With regards to severe

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hypoxaemia, meta-analysis of studies before publication of the most recent contribution of Guerin et al (Guerin 2013) strongly suggests benefit; the study of Guerin et al itself demonstrates clinically important and statistically significant benefit; and the combination of that study with other studies reaffirms that benefit. Thus although this is one of several subgroup analyses, evidence strongly favours prone positioning of mechanically ventilated patients exhibiting severe hypoxaemia.

Implications for research

Clinical practices will not be universally adopted unless data are robust (Noble 2004), but with the addition of the latest study (Guerin 2013) to this systematic review, residual uncertainty as to whether prone positioning can improve important patient-centred outcomes in patients with severe hypoxaemia has been reduced by one moderate-sized trial, as well as by this and other meta-analyses suggestive of survival benefit.

Deficiencies in current knowledge arise from:

- reliance on aggregate-level subgroup analyses to identify more specific populations that *might* better benefit from this intervention in the short term or over the longer term;
- limited data from the lung-protective ventilation era, as only four reported trials (n ˜ 830) were commenced after 2001 (Chan 2007; Fernandez 2008; Taccone 2009; Guerin 2013). Although one trial (n = 40) used a lung-protective strategy before this date (Voggenreiter 2005), investigators did not provide recorded data. These five studies account for approximately 40% of participants in this review;
- very sparse data for participants beyond six months, with available data showing no signal of benefit for prone ventilation in terms of mortality (Chiumello 2012);
- lack of sufficient functional, physiological, neuropsychological or quality of life data. Only one study of 26 patients (Chiumello 2012) has provided such data;
- lack of healthcare economics data (Sud 2011); and
- inconsistent reporting of data amongst studies, making analyses and aggregation of data for meta-analysis more difficult.

Current evidence may be enhanced by the use and publication of formal individual patient data (IPD) meta-analyses (Reade 2010; Riley 2010). Gattinoni et al (Gattinoni 2010) combined data from several studies but did not describe methodological characteristics of formal IPD meta-analyses.

With publication of the most recent study and its extraordinary results (Guerin 2013), equipoise to allow future studies to be undertaken would seem unlikely, unless long-term outcomes (12 months or longer) indicate transient benefits only. Further insights on particular groups of patients will require formal individual patient data meta-analyses rather than additional study-level analyses, as well as examination of findings beyond mortality data alone. In this regard, it is hoped that investigators in some of the trials conducted to date might be able to provide stakeholders with information regarding long-term outcomes and functional data, as has already been provided for a limited number of patients by one group of investigators (Chiumello 2012; Taccone 2009).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chan 2007

Methods	Participants were assigned to supine (n = 11) or prone (n = 11) position ventilation *according to the discretion of the physician in charge*. All participants had a Swan-Ganz catheter, and an arterial line was inserted for haemodynamic monitoring and blood sampling. Oxygen saturations were measured with a pulse oximeter. Sedation was given to all participants via continuous infusion of midazolam and neuromuscular blockade with atracurium besylate. Antibiotics were given to participants according to American Thoracic Society guidelines for CAP and based on the clinical judgement of the in-charge physician. All participants were intubated and underwent volume-controlled mechanical ventilation
Participants	22 patients with community-acquired pneumonia (fever plus cough with purulent sputum production and infiltrates on chest x-ray within 72 hours of admission) during an SARS epidemic. All patients met the criteria for ARDS as defined by the American-European Consensus Conference, with onset within 72 hours before enrolment
Interventions	Prone position ventilation vs supine

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Chan 2007 *(Continued)*

	Participants in the intervention group were ventilated in the prone position and were maintained in this position for ≥ 72 hours. Participants were turned supine once they maintained an SpO_2 > 90% with FIO_2< 60 for more than 24 hours after 72 hours of proning Tidal volume: 7.7 mL/kg IBW (95% CI ˜ 5.6 to 9.8 mL/kg IBW)
Outcomes	Primary outcomes: plasma cytokine levels at baseline and at 24 hours and 72 hours after enrolment Secondary outcomes: PaO_2/FIO_2 and complications. 14-day mortality is recorded
Notes	Randomization methods were unclear, with contradictory comments included in the manuscript and in subsequent correspondence. Described as "prospective observational study" in original paper, which also stated, "Patients were assigned to either continuous prone position ventilation (PRONE) or traditional supine ventilation (SUPINE) *a*ccording to the in-charge physician's decision." In subsequent correspondence, study authors stated, "after agreement of the in-charge physician patients were enrolled and then assigned to either PRONE or SUPINE according to a computer run randomization table" (Chan 2008). Trial was discontinued for slow enrolment due to SARS outbreak. Trial commenced in 2002, was completed in 2003 and was published in 2007 Mean of 105.6 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The conflicting statements (above) make assessment unclear
Allocation concealment (selection bias)	High risk	Bias stated by study authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Bias stated by study authors
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinded assessment not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Few endpoints and short follow-up, but comments regarding physician decisions and effects of the SARS outbreak make the risk of this sort of bias unclear
Selective reporting (reporting bias)	Unclear risk	No pre-specified protocol reported
Other bias	Low risk	No other bias identified

Chiumello 2012

Methods	Follow-up of subgroup of participants from Taccone 2009. Five Italian centres (of the 25 original centres - 23 Italian and 2 Spanish)

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Chiumello 2012 *(Continued)*

Participants	Quality of life and physiological data available for 26 participants (13 prone, 13 supine) from 67 eligible patients 12 months after enrolment. (The original study recruited 344 patients.) Mortality data from 187 patients also available
Interventions	Randomly assigned to receive supine or prone ventilation for acute respiratory distress syndrome (see Taccone 2009)
Outcomes	12-Month mortality; blood gas analysis; pulmonary function tests including CO diffusion; walking test; health-related quality of life using Short Form-36 (SF-36) and St George's Respiratory Questionnaire (SGRQ); quantitative lung CT scan analysis
Notes	Small subgroup of participants with large attrition rate; participant samples may not be representative. Low power to detect clinically meaningful differences with regards to outcomes ? Trial commenced in 2004, was completed in 2008 and was published in 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized telephone randomization system - as for main study (Taccone 2009)
Allocation concealment (selection bias)	Low risk	Centralized telephone randomization system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participants may remember and divulge allocation to "blinded" assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Very high dropout rate. 13/29 assessed in the prone group. 13/38 assessed in the supine group. Not likely to be random
Selective reporting (reporting bias)	Unclear risk	Post hoc follow-up tests
Other bias	Low risk	No other bias identified

Fernandez 2008

Methods	Multi-centre, open, randomized controlled trial over 12 months. Participants were randomly assigned by computer-generated random sequence to supine (n = 19) or early (within 48 hours) and continuous prone (n = 21) ventilation with further stratification of randomization according to severity using the SAPS II score and the type of ARDS
Participants	40 mechanically ventilated patients with early, refractory ARDS despite early protective supine ventilation 25 male, 15 female

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Fernandez 2008 *(Continued)*

	Inclusion: intubated adult patients within 48 hours of ARDS diagnosis (North American-European Consensus Conference (NAECC) criteria) Exclusion: severe hypotension requiring vasopressors (cardiovascular SOFA score 3 to 4), traumatic brain injury (TBI), unstable pelvic or spinal column fracture, moribund condition or enrolment in another trial
Interventions	After a 1-hour protocolized ventilation period, participants were placed in the assigned position (prone or supine), in which they were maintained for up to 20 hours per day. Prone participants were turned supine once PaO_2/FIO_2 quotient was < 250 mmHg (33.3 kPa) for longer than 12 hours. Mechanical ventilation appeared to be volume controlled and pressure limited Tidal volume: 7.25 mL/kg IBW (~ 95% CI 5.1 to 9.4 mL/kg IBW)
Outcomes	Primary: 60-day survival. NB ICU mortality identical, as no participant died after discharge up to the 60 days studied Secondary: length of mechanical ventilation and ICU stay
Notes	Study was prematurely stopped because of low participant recruitment. Two participants were lost to follow-up (4.8%) (1/group) and 2 supine participants were crossed over to prone. Both cross-over participants died. Criteria for new pneumonia (ventilator-associated pneumonia) not defined Trial commenced in 2003, was completed in 2004 and was published in 2008 Mean hours prone per participant not clear from text. Clarification sought but not obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized control centre produced randomization codes
Allocation concealment (selection bias)	Low risk	The above would minimize selection bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes (e.g. pressure sores) have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants lost to follow-up and 2 crossed over to prone ventilation during first week of care
Selective reporting (reporting bias)	Low risk	No mention of pre-study publication protocol, but multi-centre trial would require explicit protocol for each centre
Other bias	Unclear risk	Study was ended prematurely, and such studies have been associated with inflated effect size (Bassler 2010)

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Gattinoni 2001

Methods	Multi-centre, randomized trial over 34 consecutive months. Randomization to supine (n = 152) or prone (n = 152) position ventilation was done centrally by telephone based on a permuted block algorithm, allowing for stratification according to intensive care unit
Participants	304 mechanically ventilated patients with ALI or ARDS 214 males, 90 females Inclusion: PFR < 200 with PEEP > 5, or PFR < 300 with PEEP > 10, bilateral pulmonary infiltrates, pulmonary-capillary wedge pressure ≤ 18 mmHg or absence of clinical evidence of left atrial hypertension Exclusion: < 16 years old, cardiogenic pulmonary oedema, cerebral oedema or intracranial hypertension, proning contraindications or severe haemodynamic instability
Interventions	Participants randomly assigned to the prone group were maintained in the prone position continuously for ≥ 6 hours per day for 10 days Tidal volume: 10.3 mL/kg IBW (~ 95% CI 4.8 to 15.8 mL/kg IBW)
Outcomes	Primary: 10-day mortality (end of the prone period), mortality at discharge from ICU and 6 months post randomization Secondary: improvement in respiratory failure and organ dysfunction at 10 days
Notes	Twelve participants (7.9%) were crossed over from supine to prone position during the trial. 41 of 152 (27.0%) participants missed ≥ 1 scheduled proning sessions. Subgroup percentages were provided for more severely ill participants, etc, but not numbers of participants. Possible selection reporting bias for subgroup cutoffs (e.g. PaO_2/FIO_2 quotient of 88 mmHg (11.7 kPa). Compare these results vs the cut-off of 100 mmHg (13.3 kPa) in their recent systematic review (Gattinoni 2010). No apparent loss to follow-up and apparent strict Intention-to-treat analysis with supplementary per-protocol analyses. Trial was discontinued early by investigators and data and monitoring safety board because of slow recruitment Trial commenced in 1996, was completed in 1999 and was published in 2001 Mean of 32.9 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization - central telephone service
Allocation concealment (selection bias)	Low risk	Nothing in text to suggest selection bias following randomization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias. Pressure sore assessment was well described in this study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat listed as method of analysis. No mention of participants lost to follow-up

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Gattinoni 2001 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No mention of pre-study publication protocol, but multi-centre trial would require explicit protocol for each centre. Possible bias in reporting post hoc analyses (e.g. outcomes of participants with PaO_2/FIO_2 quotient of 88 mmHg (11.7 kPa)
Other bias	Unclear risk	Study was ended prematurely; such studies have been associated with inflated effect size (Bassler 2010), although little signal of effect was evident

Guerin 2004

Methods	Prospective, unblinded, multi-centre, randomized controlled trial over 48 consecutive months. Randomization was computer-generated and was done separately for each ICU, with participants to supine (n = 378) or prone (n = 413) position ventilation
Participants	791 participants 593 males, 198 females Inclusion: mechanical ventilation (oral or nasal tracheal intubation or tracheostomy), $PaO_2/FIO_2 \leq 300$, ≥ 18 years of age, expected duration of mechanical ventilation > 48 hours, written informed consent from next of kin Exclusion: prone position for ≥ 6 hours per day in the 4 days preceding enrolment, contraindications to proning (ICP > 30 mmHg, cerebral perfusion < 60 mmHg, massive haemoptysis, bronchopleural fistula, tracheal surgery or sternotomy in the past 15 days, MAP < 65 with or without vasopressors, DVT, pacemaker inserted for fewer than 2 days, unstable fracture), therapeutic limitation indicated in the first 24 hours of ICU admission, high risk of death in the next 48 hours, chronic respiratory failure requiring mechanical ventilation and inclusion in another protocol with mortality as a primary endpoint
Interventions	Participants were randomly assigned to the supine or the prone group, in which they were placed in a prone position for ≥ 8 hours per day Tidal volume: 10.1 mL/kg IBW* (~ 95% CI 5.5 to 14.7 mL/kg IBW). *Imputed from measured body weight data (Bloomfield 2006)
Outcomes	Primary: 28-day mortality Secondary: 90-day mortality, duration of mechanical ventilation, rate of ventilator-associated pneumonia and oxygenation
Notes	VAP was well defined; 11 of 802 participants (1.4%) recruited, lost from final analysis Trial commenced in 1998, was completed in 2002 and was published in 2004 Mean of 36.9 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Detailed methods provided
Allocation concealment (selection bias)	Low risk	Detailed methods provided

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Guerin 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 of 802 participants (1.4%) recruited, lost from final analysis
Selective reporting (reporting bias)	Low risk	Multi-centre trial - conduct and outcome measure likely agreed in advance
Other bias	High risk	Very high cross-over rates reported: "At day 28, 83 (27.9%) of 297 patients in the supine group died, 36 (44.4%) of the 81 patients who had crossed over from the supine group died, 76 (31.3%) of 243 patients in the prone group died, and 58 (34.1%) of 170 patients who crossed over from the prone group died (P value = .85)". Overall, 32% of participants in the trial were crossed over to the opposite limb of the study. This level of cross-over events makes reported effects difficult to interpret. This level of selective cross-over of participants impairs the statistical power of the study and leads to bias against a positive result (Lipsey 1990; Porta 2008)

Guerin 2013

Methods	Multi-centre, randomized, controlled, open-label trial conducted in France and Spain
Participants	ARDS - American–European Consensus Conference criteria • Endotracheal intubation and mechanical ventilation for ARDS < 36 hours • Severe ARDS (defined as PaO_2:FIO_2 ratio < 150 mmHg, with FIO_2 ≥ 0.6, PEEP ≥ 5 cm of water and tidal volume ~ 6 mL/kg ideal body weight • Confirmed after 12 to 24 hours of mechanical ventilation in the participating intensive care unit. Volume-controlled ventilation combined with PEEP table
Interventions	Prone position for ≥ 16 hours/d vs semi recumbent position Tidal volume: 6.1 mL/kg IBW (~ 95% CI 4.9 to 7.3 mL/kg IBW)
Outcomes	Primary endpoint: 28-day all-cause mortality Secondary endpoints: mortality at day 90; rate of successful extubation; time to successful extubation; length of stay in the ICU; complications; use of non-invasive ventilation; tracheotomy rate; number of days free from organ dysfunction; and ventilator settings of arterial blood gases and respiratory system mechanics measurements during the first week after randomization
Notes	30 deaths in the supine group (n = 229) had an end-of-life decision; 14 deaths in the prone group (n = 237) had an end-of-life decision. Assist/control ventilation mode is not commonly utilized in Europe. PEEP table mandated high levels of PEEP. Improved oxygenation allowed reduction of these high levels - so differential PEEP reduction of mandated PEEP may be a potential mechanism of benefit (Soni 2008) that accentuates benefit of prone positioning in this study. 8 of 474 participants recruited (1.7%) were lost from the final analysis Trial commenced in 2008, was completed in 2011 and was published in 2013

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Guerin 2013 *(Continued)*

	Mean of 68 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization - central
Allocation concealment (selection bias)	Low risk	Nothing in text to suggest post-randomization bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified. Some participants had treatment withdrawn. Prone 14/237 vs supine 30/229; bias regarding treatment is possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat listed as method of analysis. Eight participants from original cohort excluded (with explanation)
Selective reporting (reporting bias)	Low risk	Multi-centre trial - conduct and outcome measure likely agreed in advance
Other bias	Low risk	Low cross-over rate

Leal 1997

Methods	Single-centre RCT, sequential sealed envelope allocation, no cross-overs
Participants	16* patients with ARDS (8 participants per group). PaO_2/FIO_2 quotient < 150 mmHg and diagnosis to enrolment time < 24 hours (additional information from Sud 2008a) *2 additional participants were included in the actual meeting presentation (made available in Microsoft PowerPoint™ slides by Dr Jan Friederich, Toronto, Canada)
Interventions	24 hours prone ventilation (fixed duration and single application only)
Outcomes	Mortality; complications; early effects on gas exchange Tidal volume not listed
Notes	Abstract and Microsoft PowerPoint presentation of original authors supplied by Dr Jan Friederich through Professor Brian Cuthbertson. Data limited. Outcomes assumed to be short-term data in line with physiological nature of the study. Although single application lasted for 24 hours, the total application time during mechanical ventilation in the ICU was therefore limited Trial commencement and finish dates not available; abstract published in 1997. 50% of participants placed prone had airway complications despite proning only once per study participant Mortality in original abstract occurred in 5 of 7 participants in each group. With the addition of 1 participant to each group, mortality became 5 of 8 for participants randomly assigned to prone vs 6 of 8

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Leal 1997 *(Continued)*

	randomly assigned to supine. The investigation was short-term (72 hours), and mortality rates are assumed to be short-term Mean of 24 hours total prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization not stated
Allocation concealment (selection bias)	Low risk	Sequential sealed envelope allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data not described. Small single-centre study; not able to assess risk of attrition bias
Selective reporting (reporting bias)	Unclear risk	No mention of pre-study publication protocol
Other bias	Low risk	No other bias identified

Mancebo 2006

Methods	Multi-centre, randomized controlled trial over 45 months. Randomization was computer-generated, assigning participants to the supine (n = 60) or the prone (n = 76) position group. Participants were enrolled within 48 hours of tracheal intubation for severe ARDS
Participants	136 participants 86 males, 50 females Inclusion: intubation, mechanical ventilation, > 18 years of age, ARDS (American-European Consensus Conference definition), diffuse bilateral infiltrates on chest x-ray Exclusion: > 48 hours since inclusion criteria were met, participation in other trials, pregnancy, systolic BP < 80 despite vasopressors, pelvic or spinal fracture, cranial trauma and/or clinical suspicion of raised ICP, considered moribund
Interventions	Participants were randomly assigned to the supine group or to the prone group, which received continuous prone position ventilation for 20 hours per day. Mechanical ventilation with volume assist-control mode Tidal volume: 10.6 mL/kg IBW* (~ 95% CI 6.5 to 14.6 mL/kg IBW) *Correction for use of measured body weight rather than IBW (Bloomfield 2006)
Outcomes	Primary: ICU mortality

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Mancebo 2006 *(Continued)*

	Secondary: hospital mortality, associated complications and length of stay
Notes	Study was prematurely stopped because of low participant recruitment. 5 participants crossed over to prone ventilation from original assignment. (All died.) High tidal volumes were used. Up to 10 mg/kg actual body weight was allowed in the protocol and maximum plateau pressures up to 40 cm H_2O. Some participants received tidal volumes in excess of 10 mL/kg and in excess of their 2 targets of 35 and 40 cm H_2O. (See supplement.) This decreases relevance to currently accepted targets of tidal volumes of 6 mL/kg ideal body weight and plateau pressures < 30 cm H_2O. 5 cross-overs from the supine group to the prone group were reported. 6 of 142 participants (4.2%) enrolled were lost after randomization Trial commenced in 1998, was completed in 2002 and was published in 2006 Mean of 171.7 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six participants (4.2%) were not included in the final analysis: 3 because of lost forms, 2 because data were lacking and 1 as the result of transfer to a cardiac surgery centre for possible surgery
Selective reporting (reporting bias)	Low risk	No mention of pre-study publication protocol, but multi-centre trial would require an explicit protocol for each centre
Other bias	Unclear risk	Study was ended prematurely; such studies have been associated with inflated effect size (Bassler 2010)

Taccone 2009

Methods	Multi-centre, unblinded, randomized controlled trial. Randomization to the supine (n = 174) or the prone (n = 168) position group was computer-generated, and participants were stratified according to severity of hypoxaemia and participating centre. Prospective subgroup analysis defined the moderate subgroup as PaO_2/FIO_2 quotient of 100 to 200 mmHg, and severe as PaO_2/FIO_2 < 100 mmHg
Participants	342 participants 244 males, 98 females Inclusion: ARDS criteria (PFR ≤ 200 mmHg for PEEP 5 to 10 cm H_2O)

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Taccone 2009 *(Continued)*

	Exclusion: < 16 yo, > 72 hours since diagnosis of ARDS, history of solid organ or bone marrow transplantation, contraindication to proning (raised ICP, spine/pelvic fracture)
Interventions	Participants were randomly assigned to supine or prone position ventilation, which required maintaining prone position ≥ 20 hours per day until resolution of ARDS or the end of the 28-day study period Tidal volume: 8.0 mL/kg IBW (~ 95% CI 4.7 to 11.3 mL/kg IBW)
Outcomes	Primary: 28-day all-cause mortality Secondary: 6-month and ICU discharge mortality, organ dysfunction, complication rate related to prone positioning
Notes	It is noted that more participants randomly assigned to prone ventilation received increased sedation or muscle relaxants. This co-intervention can improve survival (Papazian 2010) Trial commenced in 2004, was completed in 2008 and was published in 2009. Participants were enrolled a median of 0 days (IQR 0 to 1) after mechanical ventilation. 20 participants (11.5%) randomly assigned to the supine position were crossed over to the prone group as rescue therapy for hypoxaemia. 34 participants (20.2%) assigned to prone did not receive the intervention but were included in the ITT analysis. Ventilator-associated pneumonia was not defined Mean of 149.4 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized telephone randomization system
Allocation concealment (selection bias)	Low risk	Centralized telephone randomization system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants in each group were lost to follow-up. All 4 were assumed alive for the follow-up period. 2 additional participants (1 per group) was ineligible; both were removed before protocol initiation
Selective reporting (reporting bias)	Low risk	Protocol published
Other bias	Unclear risk	11.5% of participants randomly assigned to supine position were crossed over to the prone position as part of the pre-defined rescue protocol. 34 participants (20.2%) assigned to prone did not receive intervention but were included in the ITT analysis

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Voggenreiter 2005

Methods	2 (trauma)-centre prospective randomized trial. Randomization assigned participants to supine (n = 19) or prone (n = 21) position group and was conducted centrally by telephone, using a permuted-block algorithm, allowing for stratification according to ICU, participant age, ISS, AIS-chest, AIS-head and interval between injury and randomization
Participants	40 participants 33 males, 7 females Inclusion: multiple trauma patients 18 to 80 years of age; ISS > 16; *modified* ALI/ARDS criteria (PaO_2/FIO_2 quotient for ALI or ARDS; "lung infiltrates"; and absence of evidence of left atrial hypertension) Exclusion: cardiogenic pulmonary oedema, cerebral oedema, ↑ ICP, other contraindications to prone (e.g. haemodynamic instability, unstable fracture)
Interventions	Participants were randomly assigned to the supine or the prone ventilation group, in which participants were continuously maintained in the prone position ≥ 8 hours and for a maximum of 23 hours per day. Mean of 11 hours (SD 5) of prone applied, and applied on a mean of 7 (SD 4) occasions
Outcomes	Primary: duration of mechanical ventilation Secondary: days with ARDS (PaO_2:FIO_2 < 200), ALI (PaO_2:FIO_2 200 to 300); days with LIS > 2, course of PaO_2:FIO_2, Qs/Qt score, total static lung compliance, PIP, PEEP, LIS, TISS-28, SOFA score, sepsis, prevalence of pneumonia, mortality within the 90-day study period, complications/adverse events and ARDS following ALI
Notes	Participants in the supine limb received 3 times as many packed red cells (mean of 28.2 vs 9.5 packs of red cells per participant) (i.e. 19 more packs of red cells per participant, on average). Possible fluid overload and effects of RCC on infection and leucocytosis could confound pneumonia diagnosis. Neuromuscular blockers were used more in participants ventilated prone (7.8 days/patient vs 5.6 days/patient; P value = 0.06). Neuromuscular blockade is an intervention that could independently improve mortality (Papazian 2010) Trial commenced in 1999, was completed in 2001 and was published in 2005. A variety of modes of ventilation were used: BIPAP (n = 19), CPPV (n = 20) and SIMV (n = 1), but "lung protective strategy" was used. Actual data for tidal volumes are not available. Listed as enrolled < 48 hours from meeting criteria (Sud 2010). Pneumonia (VAP), new pneumonia within 90 days - reasonably well-defined criteria - but results could be affected by differential RCC transfusion, as noted above. No apparent loss to follow-up Mean of 77 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized telephone randomization system
Allocation concealment (selection bias)	Low risk	Centralized telephone randomization system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias

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Voggenreiter 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No published protocol. 2-centre study
Other bias	High risk	Markedly different red cell transfusion rates for 2 groups of participants (high risk). Sample size not predefined (unclear risk)

AIS = Abbreviated injury scale; ALI = Acute lung injury; ARDS = Acute respiratory distress syndrome; BIPAP = Bi-phasic positive airways pressure; BP = Blood pressure; CAP = Community-acquired pneumonia; CO = Cardiac output; CPPV = Controlled positive-pressure ventilation; CT = Computed tomography; DVT = Deep venous thrombosis; IBW = Predicted ideal body weight; ICP = Intracranial pressure; ICU = Intensive care unit; ISS = Injury severity score; ITT = Intention-to-treat; IQR = Interquartile range; LIS = Lung injury score; MAP = Mean arterial pressure; n = number; NAECC = North American-European Consensus Criteria; NB = Note well; PEEP = Positive end-expiratory pressure; PFR = Pulmonary arterial-fractional inspired oxygen ratio; PIP = Peak inspiratory pressure; RCC = Red cell concentrate; RCT = Randomized controlled trial; SAPS = Simplified acute physiology score; SARS = Severe acute respiratory syndrome; SD = Standard deviation; SF-36 = Short Form-36; SGRQ = St George's Respiratory Questionnaire; SIMV = Synchronized intermittent mechanical ventilation; SOFA = Sequential organ failure assessment; TBI = Traumatic brain injury; TISS = Therapeutic intervention scoring system; VAP = Ventilator-associated pneumonia.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beuret 2002	Prone position was used for prevention rather than as treatment for hypoxaemic respiratory failure. Mean PaO_2/FIO_2 quotient exceeded 40 kPa (300 mmHg) in both groups. Total hours prone for duration of study = 24 (4 hours for 6.0 days)
Curley 2005	This study has been incorporated into other meta-analyses. However, the study population (n = 102) predominantly consisted of very young children, with 49% ≤ 2 years of age and 73% ≤ 8 years of age. Our protocol specifically excluded children (Bloomfield 2009)
Demory 2007	Non-conventional ventilation employed: 12 hours of high-frequency oscillatory ventilation (HFOV) following 12 hours of conventional ventilation in the prone or the supine position. Non-conventional ventilation was specifically excluded from our protocol. Treatment interaction could not be excluded, as not a factorial design (Fleiss 1986; Friedman 1998). Total hours prone in study = 12 (12 hours prone for 1 day)
Papazian 2005	Non-conventional ventilation employed: comparison of non-conventional mechanical ventilation vs high-frequency oscillatory ventilation (HFOV) used in 12-hour protocol only Non-conventional ventilation was specifically excluded from our protocol. Treatment interaction could not be excluded, as not a factorial design (Fleiss 1986; Friedman 1998). Total hours prone = 12 (12 hours prone for 1 day only)
Watanabe 2002	Infusion of muscle relaxants given to prone participants; this co-intervention is associated with improved survival in patients with lung injury (Papazian 2010). Mortality outcomes not published

HFOV = High-frequency oscillatory ventilation; n = number.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ayzac 2014

Methods	Further analysis of PROSEVA randomized controlled trial (Guerin 2013)

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Ayzac 2014 *(Continued)*

Participants	
Interventions	
Outcomes	Ventilator-associated pneumonia
Notes	Abstract from European Society of Intensive Care meeting. May provide information on a secondary outcome

Girard 2014

Methods	Further analysis of PROSEVA randomized controlled trial (Guerin 2013)
Participants	
Interventions	
Outcomes	Pressure ulcers
Notes	May provide information on a secondary outcome

Hu 2014

Methods	Systematic review of prone positioning
Participants	
Interventions	
Outcomes	
Notes	May provide further information

Park 2015

Methods	Systematic review of prone positioning
Participants	
Interventions	
Outcomes	
Notes	May provide further information. Does not mention or include the study of Zhou 2014

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Zhou 2014

Methods	Randomized controlled trial of prone position vs supine position and with use of recruitment manoeuvres
Participants	116 patients with severe acute respiratory distress syndrome
Interventions	Prone positioning and recruitment manoeuvres
Outcomes	28-Day mortality; ventilation days; ICU length of stay
Notes	Abstract in English. Article in Chinese. New data, and may have impact on analysis if co-intervention of recruitment manoeuvres equally applied to both supine and prone groups

ICU = Intensive care unit.

DATA AND ANALYSES

Comparison 1. Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Short-term mortality	8	2117	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.69, 1.02]
1.2 Longer-term mortality	8	2140	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.03]
2 Sub-group analysis (SGA) of mortality < 16 hours/d prone	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Short-term mortality	2	1095	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.89, 1.21]
2.2 Longer-term mortality	3	1135	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.92, 1.17]
3 SGA of mortality prone ≥ 16 hours/d	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Short-term mortality	6	1022	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.58, 0.93]
3.2 Longer-term mortality prone	5	1005	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.99]
4 SGA of mortality: enrolled ≤ 48 hours after entry criteria met/ventilation	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Short-term mortality	5	1000	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.93]
4.2 Longer-term mortality	5	1024	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.94]
5 SGA of mortality: enrolled > 48 hours after entry criteria met/ventilation	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Short-term mortality	3	1117	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.89, 1.21]

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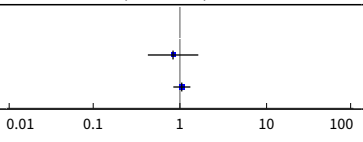
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.2 Longer-term mortality	3	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.17]
6 SGA of severe hypoxaemia at entry	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Short-term mortality	6	744	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.95]
6.2 Longer-term mortality	7	977	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.65, 0.92]
7 SGA of less severe hypoxaemia at entry	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Short-term mortality	4	1095	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.21]
7.2 Longer-term mortality	6	1108	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.93, 1.21]
8 SGA of SAPS II ≤ 49/≥ 50: short-term mortality	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 SAPS II ≤ 49	2	327	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.45, 1.60]
8.2 SAPS II ≥ 50	2	113	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.25, 1.40]
9 SGA of low tidal volume (mean 6 to 8 mL/kg IBW)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Short-term mortality	3	830	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.43, 1.20]
9.2 Longer-term mortality	5	911	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.96]
10 SGA of high tidal volume (> 8 mL/kg IBW)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Short-term mortality	3	1231	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.86, 1.14]
10.2 Longer-term mortality	3	1231	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.90, 1.13]
11 SGA of ARDS only	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Short-term mortality	7	1326	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.63, 1.00]
11.2 Longer-term mortality	8	1758	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.71, 1.01]

Analysis 1.1. Comparison 1 Mortality, Outcome 1 Mortality.

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Short-term mortality					
Leal 1997	5/8	6/8		6.52%	0.83[0.43,1.63]
Gattinoni 2001	77/152	73/152		18.66%	1.05[0.84,1.32]



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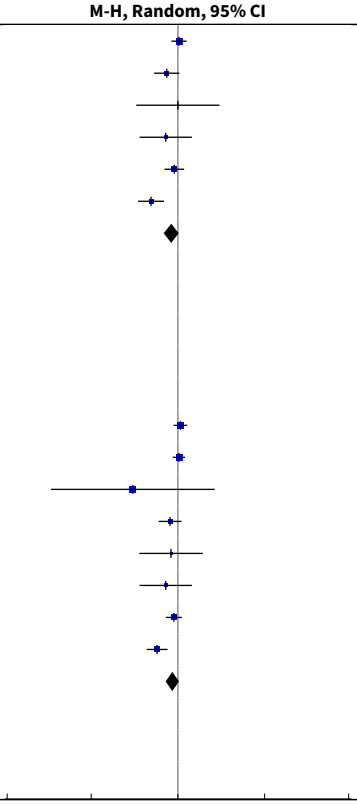
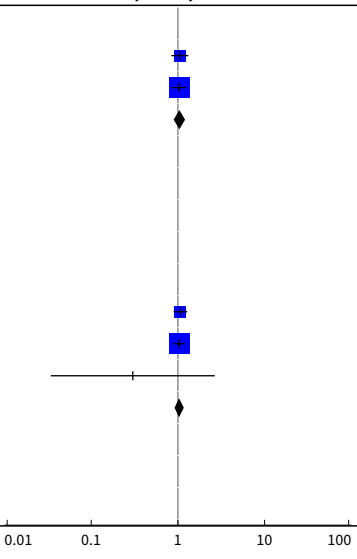
Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Guerin 2004	134/413	119/378		19.63%	1.03[0.84,1.26]
Mancebo 2006	33/76	35/60		14.57%	0.74[0.53,1.04]
Chan 2007	4/11	4/11		2.87%	1[0.33,3.02]
Fernandez 2008	8/21	10/19		6.2%	0.72[0.36,1.45]
Taccone 2009	64/168	73/174		17.38%	0.91[0.7,1.18]
Guerin 2013	38/237	75/229		14.17%	0.49[0.35,0.69]
Subtotal (95% CI)	**1086**	**1031**		**100%**	**0.84[0.69,1.02]**
Total events: 363 (Prone group), 395 (Supine group)					
Heterogeneity: Tau^2=0.04; Chi^2=17.29, df=7(P=0.02); I^2=59.53%					
Test for overall effect: Z=1.74(P=0.08)					
1.1.2 Longer-term mortality					
Gattinoni 2001	96/152	90/152		20.31%	1.07[0.89,1.28]
Guerin 2004	179/413	159/377		21.14%	1.03[0.87,1.21]
Voggenreiter 2005	1/21	3/19		0.64%	0.3[0.03,2.66]
Mancebo 2006	38/76	37/60		14.69%	0.81[0.6,1.1]
Chan 2007	5/11	6/11		3.72%	0.83[0.36,1.94]
Fernandez 2008	8/21	10/19		5.16%	0.72[0.36,1.45]
Taccone 2009	79/168	91/174		18.62%	0.9[0.73,1.11]
Guerin 2013	56/237	94/229		15.72%	0.58[0.44,0.76]
Subtotal (95% CI)	**1099**	**1041**		**100%**	**0.86[0.72,1.03]**
Total events: 462 (Prone group), 490 (Supine group)					
Heterogeneity: Tau^2=0.03; Chi^2=18.05, df=7(P=0.01); I^2=61.21%					
Test for overall effect: Z=1.67(P=0.1)					



Analysis 1.2. Comparison 1 Mortality, Outcome 2 Sub-group analysis (SGA) of mortality < 16 hours/d prone.

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Short-term mortality					
Gattinoni 2001	77/152	73/152		37.01%	1.05[0.84,1.32]
Guerin 2004	134/413	119/378		62.99%	1.03[0.84,1.26]
Subtotal (95% CI)	**565**	**530**		**100%**	**1.04[0.89,1.21]**
Total events: 211 (Prone group), 192 (Supine group)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=0.5(P=0.62)					
1.2.2 Longer-term mortality					
Gattinoni 2001	96/152	90/152		34.72%	1.07[0.89,1.28]
Guerin 2004	179/413	159/378		64.06%	1.03[0.88,1.21]
Voggenreiter 2005	1/21	3/19		1.22%	0.3[0.03,2.66]
Subtotal (95% CI)	**586**	**549**		**100%**	**1.03[0.92,1.17]**
Total events: 276 (Prone group), 252 (Supine group)					
Heterogeneity: Tau^2=0; Chi^2=1.35, df=2(P=0.51); I^2=0%					
Test for overall effect: Z=0.54(P=0.59)					



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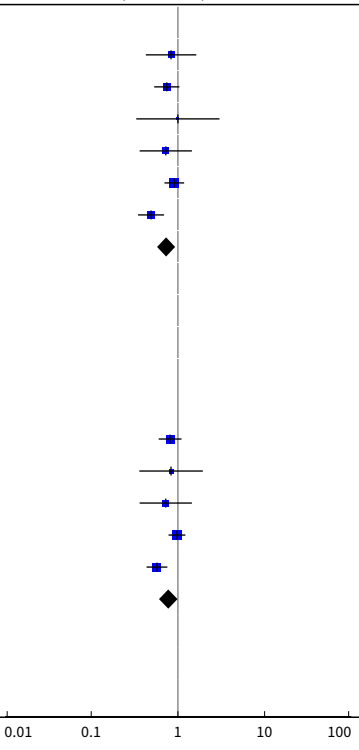
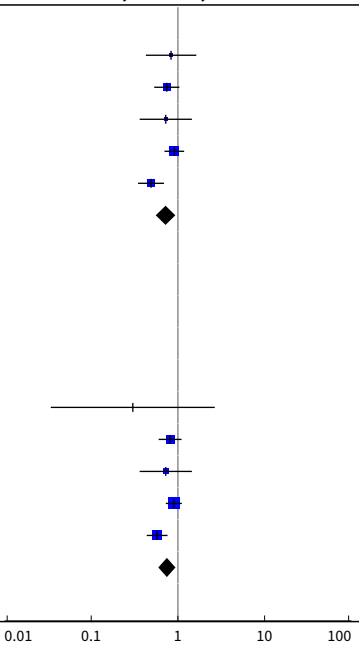
Analysis 1.3. Comparison 1 Mortality, Outcome 3 SGA of mortality prone ≥ 16 hours/d.

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Short-term mortality					
Leal 1997	5/8	6/8		9.96%	0.83[0.43,1.63]
Mancebo 2006	33/76	35/60		23.91%	0.74[0.53,1.04]
Chan 2007	4/11	4/11		4.26%	1[0.33,3.02]
Fernandez 2008	8/21	10/19		9.46%	0.72[0.36,1.45]
Taccone 2009	64/168	73/174		29.25%	0.91[0.7,1.18]
Guerin 2013	38/237	75/229		23.17%	0.49[0.35,0.69]
Subtotal (95% CI)	**521**	**501**		**100%**	**0.73[0.58,0.93]**
Total events: 152 (Prone group), 203 (Supine group)					
Heterogeneity: Tau²=0.03; Chi²=8.49, df=5(P=0.13); I²=41.11%					
Test for overall effect: Z=2.56(P=0.01)					
1.3.2 Longer-term mortality prone					
Mancebo 2006	38/76	37/60		25.46%	0.81[0.6,1.1]
Chan 2007	5/11	6/11		7.07%	0.83[0.36,1.94]
Fernandez 2008	8/21	10/19		9.67%	0.72[0.36,1.45]
Taccone 2009	79/168	84/174		30.75%	0.97[0.78,1.22]
Guerin 2013	56/237	94/228		27.05%	0.57[0.43,0.76]
Subtotal (95% CI)	**513**	**492**		**100%**	**0.77[0.61,0.99]**
Total events: 186 (Prone group), 231 (Supine group)					
Heterogeneity: Tau²=0.04; Chi²=8.89, df=4(P=0.06); I²=54.99%					
Test for overall effect: Z=2.04(P=0.04)					



Analysis 1.4. Comparison 1 Mortality, Outcome 4 SGA of mortality: enrolled ≤ 48 hours after entry criteria met/ventilation.

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Short-term mortality					
Leal 1997	5/8	6/8		11.1%	0.83[0.43,1.63]
Mancebo 2006	33/76	35/60		24.76%	0.74[0.53,1.04]
Fernandez 2008	8/21	10/19		10.56%	0.72[0.36,1.45]
Taccone 2009	64/168	73/174		29.5%	0.91[0.7,1.18]
Guerin 2013	38/237	75/229		24.08%	0.49[0.35,0.69]
Subtotal (95% CI)	**510**	**490**		**100%**	**0.72[0.56,0.93]**
Total events: 148 (Prone group), 199 (Supine group)					
Heterogeneity: Tau²=0.04; Chi²=8.21, df=4(P=0.08); I²=51.29%					
Test for overall effect: Z=2.47(P=0.01)					
1.4.2 Longer-term mortality					
Voggenreiter 2005	1/21	3/19		1.07%	0.3[0.03,2.66]
Mancebo 2006	38/76	37/60		26.69%	0.81[0.6,1.1]
Fernandez 2008	8/21	10/19		8.91%	0.72[0.36,1.45]
Taccone 2009	79/168	91/174		34.58%	0.9[0.73,1.11]
Guerin 2013	56/237	94/229		28.74%	0.58[0.44,0.76]
Subtotal (95% CI)	**523**	**501**		**100%**	**0.75[0.59,0.94]**
Total events: 182 (Prone group), 235 (Supine group)					



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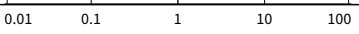
Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.03; Chi²=7.37, df=4(P=0.12); I²=45.69%					
Test for overall effect: Z=2.52(P=0.01)					

Analysis 1.5. Comparison 1 Mortality, Outcome 5 SGA of mortality: enrolled > 48 hours after entry criteria met/ventilation.

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Short-term mortality					
Gattinoni 2001	77/152	73/152		36.27%	1.05[0.84,1.32]
Guerin 2004	134/413	119/378		61.74%	1.03[0.84,1.26]
Chan 2007	4/11	4/11		1.99%	1[0.33,3.02]
Subtotal (95% CI)	**576**	**541**		**100%**	**1.04[0.89,1.21]**
Total events: 215 (Prone group), 196 (Supine group)					
Heterogeneity: Tau²=0; Chi²=0.03, df=2(P=0.99); I²=0%					
Test for overall effect: Z=0.49(P=0.62)					
1.5.2 Longer-term mortality					
Gattinoni 2001	96/152	90/152		34.32%	1.07[0.89,1.28]
Guerin 2004	179/413	159/377		63.39%	1.03[0.87,1.21]
Chan 2007	5/11	6/11		2.29%	0.83[0.36,1.94]
Subtotal (95% CI)	**576**	**540**		**100%**	**1.04[0.92,1.17]**
Total events: 280 (Prone group), 255 (Supine group)					
Heterogeneity: Tau²=0; Chi²=0.37, df=2(P=0.83); I²=0%					
Test for overall effect: Z=0.58(P=0.56)					



Analysis 1.6. Comparison 1 Mortality, Outcome 6 SGA of severe hypoxaemia at entry.

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Short-term mortality					
Leal 1997	5/8	6/8		4.99%	0.83[0.43,1.63]
Gattinoni 2001	32/53	30/46		24.27%	0.93[0.68,1.25]
Guerin 2004	43/90	40/75		24.43%	0.9[0.66,1.21]
Mancebo 2006	19/43	19/29		12.24%	0.67[0.44,1.03]
Taccone 2009	34/74	42/76		21.91%	0.83[0.6,1.14]
Guerin 2013	25/121	41/121		12.16%	0.61[0.4,0.94]
Subtotal (95% CI)	**389**	**355**		**100%**	**0.82[0.7,0.95]**
Total events: 158 (Prone group), 178 (Supine group)					
Heterogeneity: Tau²=0; Chi²=3.7, df=5(P=0.59); I²=0%					
Test for overall effect: Z=2.67(P=0.01)					
1.6.2 Longer-term mortality					
Gattinoni 2001	35/53	35/46		21.19%	0.87[0.67,1.12]
Guerin 2004	53/90	49/75		22.28%	0.9[0.71,1.14]

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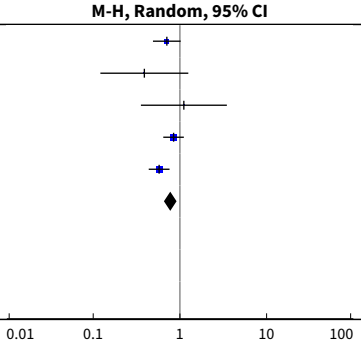
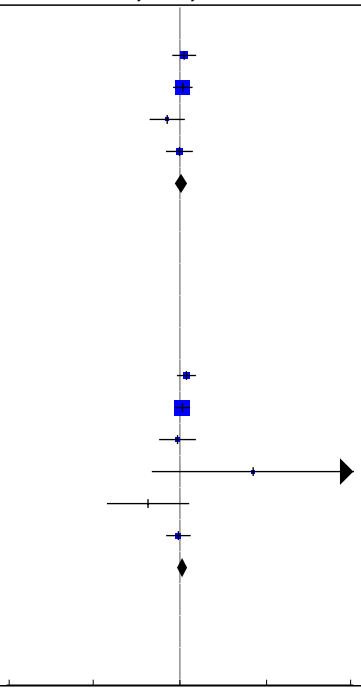
Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Mancebo 2006	22/43	21/29		13.75%	0.71[0.49,1.02]
Chan 2007	2/6	6/7		1.96%	0.39[0.12,1.25]
Fernandez 2008	5/9	2/4		2.06%	1.11[0.36,3.48]
Taccone 2009	39/73	48/76		19.46%	0.85[0.64,1.11]
Guerin 2013	56/237	94/229		19.31%	0.58[0.44,0.76]
Subtotal (95% CI)	**511**	**466**		**100%**	**0.77[0.65,0.92]**
Total events: 212 (Prone group), 255 (Supine group)					
Heterogeneity: Tau²=0.02; Chi²=9.81, df=6(P=0.13); I²=38.85%					
Test for overall effect: Z=2.99(P=0)					



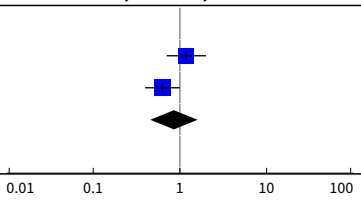
Analysis 1.7. Comparison 1 Mortality, Outcome 7 SGA of less severe hypoxaemia at entry.

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Short-term mortality					
Gattinoni 2001	45/99	43/106		23%	1.12[0.82,1.54]
Guerin 2004	91/323	79/303		45.15%	1.08[0.84,1.4]
Mancebo 2006	18/43	17/29		11.25%	0.71[0.45,1.14]
Taccone 2009	36/94	38/98		20.61%	0.99[0.69,1.41]
Subtotal (95% CI)	**559**	**536**		**100%**	**1.03[0.87,1.21]**
Total events: 190 (Prone group), 177 (Supine group)					
Heterogeneity: Tau²=0; Chi²=2.83, df=3(P=0.42); I²=0%					
Test for overall effect: Z=0.35(P=0.73)					
1.7.2 Longer-term mortality					
Gattinoni 2001	57/95	52/103		21.7%	1.19[0.92,1.53]
Guerin 2004	126/323	110/302		49.45%	1.07[0.88,1.31]
Mancebo 2006	16/33	16/31		7.18%	0.94[0.58,1.53]
Chan 2007	3/4	0/4		0.22%	7[0.47,103.27]
Fernandez 2008	3/12	7/12		3.04%	0.43[0.14,1.28]
Taccone 2009	40/93	43/96		18.41%	0.96[0.7,1.33]
Subtotal (95% CI)	**560**	**548**		**100%**	**1.06[0.93,1.21]**
Total events: 245 (Prone group), 228 (Supine group)					
Heterogeneity: Tau²=0; Chi²=5.93, df=5(P=0.31); I²=15.75%					
Test for overall effect: Z=0.84(P=0.4)					



Analysis 1.8. Comparison 1 Mortality, Outcome 8 SGA of SAPS II ≤ 49/≥ 50: short-term mortality.

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 SAPS II ≤ 49					
Gattinoni 2001	23/105	22/119		48.06%	1.18[0.7,2]
Mancebo 2006	18/54	26/49		51.94%	0.63[0.4,1]
Subtotal (95% CI)	**159**	**168**		**100%**	**0.85[0.45,1.6]**
Total events: 41 (Prone group), 48 (Supine group)					



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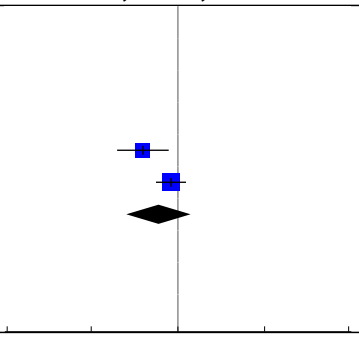
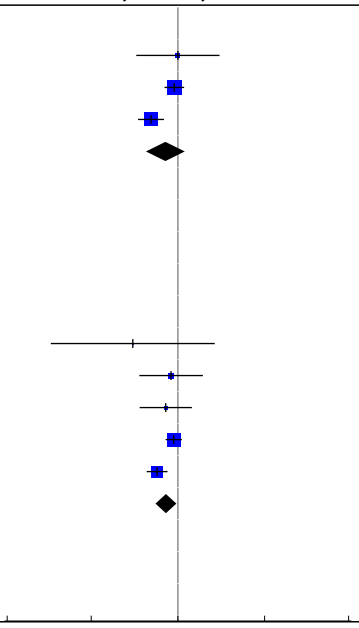
Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.14; Chi²=3.26, df=1(P=0.07); I²=69.34%					
Test for overall effect: Z=0.5(P=0.62)					
1.8.2 SAPS II ≥ 50					
Gattinoni 2001	9/47	16/33		44.73%	0.39[0.2,0.78]
Mancebo 2006	15/22	9/11		55.27%	0.83[0.56,1.24]
Subtotal (95% CI)	**69**	**44**		**100%**	**0.6[0.25,1.4]**
Total events: 24 (Prone group), 25 (Supine group)					
Heterogeneity: Tau²=0.3; Chi²=4.68, df=1(P=0.03); I²=78.63%					
Test for overall effect: Z=1.19(P=0.24)					



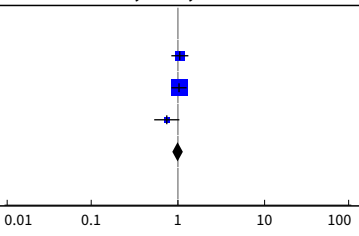
Analysis 1.9. Comparison 1 Mortality, Outcome 9 SGA of low tidal volume (mean 6 to 8 mL/kg IBW).

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Short-term mortality					
Chan 2007	4/11	4/11		15.13%	1[0.33,3.02]
Taccone 2009	64/168	73/174		44.18%	0.91[0.7,1.18]
Guerin 2013	38/237	75/229		40.69%	0.49[0.35,0.69]
Subtotal (95% CI)	**416**	**414**		**100%**	**0.72[0.43,1.2]**
Total events: 106 (Prone group), 152 (Supine group)					
Heterogeneity: Tau²=0.14; Chi²=8.35, df=2(P=0.02); I²=76.05%					
Test for overall effect: Z=1.27(P=0.2)					
1.9.2 Longer-term mortality					
Voggenreiter 2005	1/21	3/19		1.58%	0.3[0.03,2.66]
Chan 2007	5/11	6/11		9.08%	0.83[0.36,1.94]
Fernandez 2008	8/21	10/19		12.45%	0.72[0.36,1.45]
Taccone 2009	79/169	91/174		41.34%	0.89[0.72,1.11]
Guerin 2013	56/237	94/229		35.55%	0.58[0.44,0.76]
Subtotal (95% CI)	**459**	**452**		**100%**	**0.73[0.55,0.96]**
Total events: 149 (Prone group), 204 (Supine group)					
Heterogeneity: Tau²=0.04; Chi²=7.05, df=4(P=0.13); I²=43.23%					
Test for overall effect: Z=2.25(P=0.02)					



Analysis 1.10. Comparison 1 Mortality, Outcome 10 SGA of high tidal volume (> 8 mL/kg IBW).

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Short-term mortality					
Gattinoni 2001	77/152	73/152		30.88%	1.05[0.84,1.32]
Guerin 2004	134/413	119/378		52.57%	1.03[0.84,1.26]
Mancebo 2006	33/76	35/60		16.55%	0.74[0.53,1.04]
Subtotal (95% CI)	**641**	**590**		**100%**	**0.99[0.86,1.14]**
Total events: 244 (Prone group), 227 (Supine group)					



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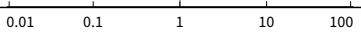
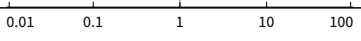
Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=3.25, df=2(P=0.2); I²=38.43%					
Test for overall effect: Z=0.13(P=0.9)					
1.10.2 Longer-term mortality					
Gattinoni 2001	96/152	90/152		30.26%	1.07[0.89,1.28]
Guerin 2004	179/413	159/378		55.83%	1.03[0.88,1.21]
Mancebo 2006	38/76	37/60		13.91%	0.81[0.6,1.1]
Subtotal (95% CI)	**641**	**590**		**100%**	**1.01[0.9,1.13]**
Total events: 313 (Prone group), 286 (Supine group)					
Heterogeneity: Tau²=0; Chi²=2.47, df=2(P=0.29); I²=18.91%					
Test for overall effect: Z=0.19(P=0.85)					



Analysis 1.11. Comparison 1 Mortality, Outcome 11 SGA of ARDS only.

Study or subgroup	Prone group n/N	Supine group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Short-term mortality					
Leal 1997	5/8	6/8		8.42%	0.83[0.43,1.63]
Gattinoni 2001	77/152	75/152		22.83%	1.03[0.82,1.29]
Mancebo 2006	33/76	35/60		18.08%	0.74[0.53,1.04]
Chan 2007	4/11	4/11		3.77%	1[0.33,3.02]
Fernandez 2008	8/21	10/19		8.02%	0.72[0.36,1.45]
Taccone 2009	64/168	73/174		21.26%	0.91[0.7,1.18]
Guerin 2013	38/237	75/229		17.61%	0.49[0.35,0.69]
Subtotal (95% CI)	**673**	**653**		**100%**	**0.79[0.63,1]**
Total events: 229 (Prone group), 278 (Supine group)					
Heterogeneity: Tau²=0.05; Chi²=13.9, df=6(P=0.03); I²=56.84%					
Test for overall effect: Z=2(P=0.05)					
1.11.2 Longer-term mortality					
Gattinoni 2001	92/148	87/149		20.88%	1.06[0.88,1.28]
Guerin 2004	98/230	81/183		18.97%	0.96[0.77,1.2]
Voggenreiter 2005	1/21	3/19		0.63%	0.3[0.03,2.66]
Mancebo 2006	38/76	37/60		15.1%	0.81[0.6,1.1]
Chan 2007	5/11	6/11		3.72%	0.83[0.36,1.94]
Fernandez 2008	8/21	10/19		5.18%	0.72[0.36,1.45]
Taccone 2009	79/168	91/176		19.31%	0.91[0.73,1.13]
Guerin 2013	56/237	94/229		16.21%	0.58[0.44,0.76]
Subtotal (95% CI)	**912**	**846**		**100%**	**0.85[0.71,1.01]**
Total events: 377 (Prone group), 409 (Supine group)					
Heterogeneity: Tau²=0.03; Chi²=15.84, df=7(P=0.03); I²=55.81%					
Test for overall effect: Z=1.85(P=0.07)					



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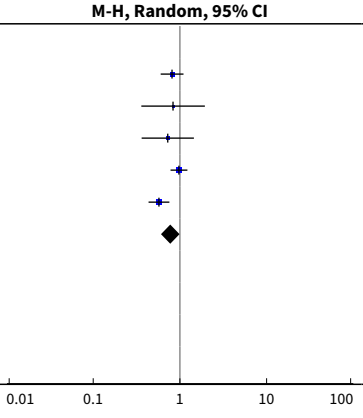
Comparison 2. Intervention comparisons and interactions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Longer duration vs shorter duration of proning: longer-term mortality	8	2140	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.73, 1.04]
1.1 > 16 hours	5	1005	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.99]
1.2 ≤ 16 hours prone	3	1135	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.18]
2 Early enrolment vs later enrolment to intervention: longer-term mortality	8	2140	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.03]
2.1 Early enrolment ≤ 48 hours	5	1024	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.94]
2.2 Late enrolment > 48 hours	3	1116	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.17]
3 Severe vs less-severe hypoxaemia: longer-term mortality	7	2085	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.03]
3.1 Severe hypoxaemia	7	977	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.65, 0.92]
3.2 Less severe hypoxaemia	6	1108	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.92, 1.26]
4 Lower tidal volume (TV) ventilation vs higher TV ventilation: longer-term mortality	8	2183	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
4.1 Lower TV - mean 6 to 8 mL/kg IBW	5	911	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.96]
4.2 High TV - mean > 8 mL/kg IBW	4	1272	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]

Analysis 2.1. Comparison 2 Intervention comparisons and interactions, Outcome 1 Longer duration vs shorter duration of proning: longer-term mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 > 16 hours					
Mancebo 2006	38/76	37/60		14.81%	0.81[0.6,1.1]
Chan 2007	5/11	6/11		3.84%	0.83[0.36,1.94]
Fernandez 2008	8/21	10/19		5.3%	0.72[0.36,1.45]
Taccone 2009	79/168	84/174		18.26%	0.97[0.78,1.22]
Guerin 2013	56/237	94/228		15.83%	0.57[0.43,0.76]
Subtotal (95% CI)	**513**	**492**		**58.05%**	**0.77[0.61,0.99]**
Total events: 186 (Experimental), 231 (Control)					
Heterogeneity: Tau²=0.04; Chi²=8.89, df=4(P=0.06); I²=54.99%					
Test for overall effect: Z=2.04(P=0.04)					



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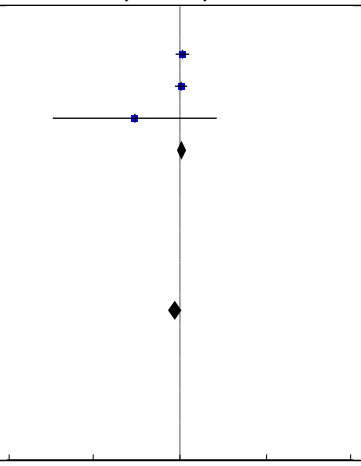
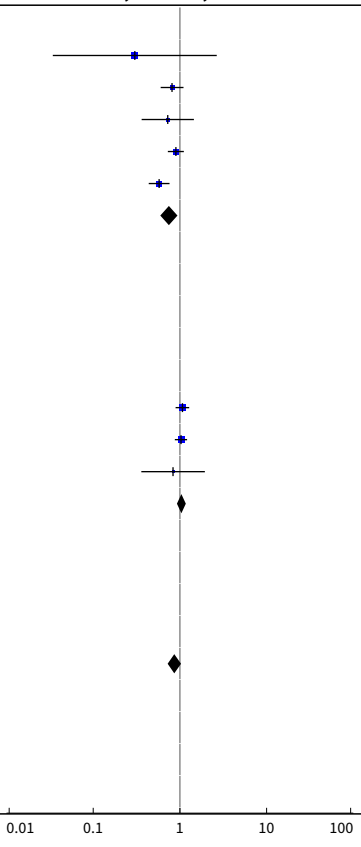
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.2 ≤ 16 hours prone					
Gattinoni 2001	96/152	90/152		20.25%	1.07[0.89,1.28]
Guerin 2004	179/413	159/378		21.04%	1.03[0.88,1.21]
Voggenreiter 2005	1/21	3/19		0.66%	0.3[0.03,2.66]
Subtotal (95% CI)	**586**	**549**		**41.95%**	**1.04[0.92,1.18]**
Total events: 276 (Experimental), 252 (Control)					
Heterogeneity: Tau²=0; Chi²=1.35, df=2(P=0.51); I²=0%					
Test for overall effect: Z=0.68(P=0.5)					
Total (95% CI)	**1099**	**1041**		**100%**	**0.87[0.73,1.04]**
Total events: 462 (Experimental), 483 (Control)					
Heterogeneity: Tau²=0.03; Chi²=18.48, df=7(P=0.01); I²=62.11%					
Test for overall effect: Z=1.49(P=0.13)					
Test for subgroup differences: Chi²=4.54, df=1 (P=0.03), I²=77.99%					



Analysis 2.2. Comparison 2 Intervention comparisons and interactions, Outcome 2 Early enrolment vs later enrolment to intervention: longer-term mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Early enrolment ≤ 48 hours					
Voggenreiter 2005	1/21	3/19		0.64%	0.3[0.03,2.66]
Mancebo 2006	38/76	37/60		14.69%	0.81[0.6,1.1]
Fernandez 2008	8/21	10/19		5.16%	0.72[0.36,1.45]
Taccone 2009	79/168	91/174		18.62%	0.9[0.73,1.11]
Guerin 2013	56/237	94/229		15.72%	0.58[0.44,0.76]
Subtotal (95% CI)	**523**	**501**		**54.83%**	**0.75[0.59,0.94]**
Total events: 182 (Experimental), 235 (Control)					
Heterogeneity: Tau²=0.03; Chi²=7.37, df=4(P=0.12); I²=45.69%					
Test for overall effect: Z=2.52(P=0.01)					
2.2.2 Late enrolment > 48 hours					
Gattinoni 2001	96/152	90/152		20.31%	1.07[0.89,1.28]
Guerin 2004	179/413	159/377		21.14%	1.03[0.87,1.21]
Chan 2007	5/11	6/11		3.72%	0.83[0.36,1.94]
Subtotal (95% CI)	**576**	**540**		**45.17%**	**1.04[0.92,1.17]**
Total events: 280 (Experimental), 255 (Control)					
Heterogeneity: Tau²=0; Chi²=0.37, df=2(P=0.83); I²=0%					
Test for overall effect: Z=0.65(P=0.52)					
Total (95% CI)	**1099**	**1041**		**100%**	**0.86[0.72,1.03]**
Total events: 462 (Experimental), 490 (Control)					
Heterogeneity: Tau²=0.03; Chi²=18.05, df=7(P=0.01); I²=61.21%					
Test for overall effect: Z=1.67(P=0.1)					
Test for subgroup differences: Chi²=6.43, df=1 (P=0.01), I²=84.44%					



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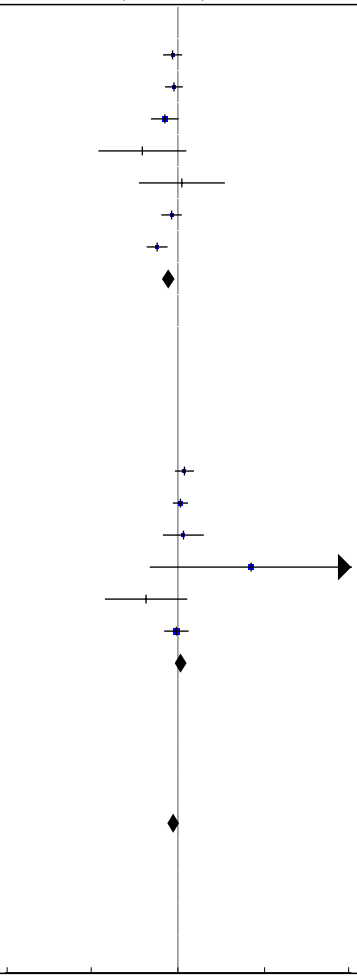
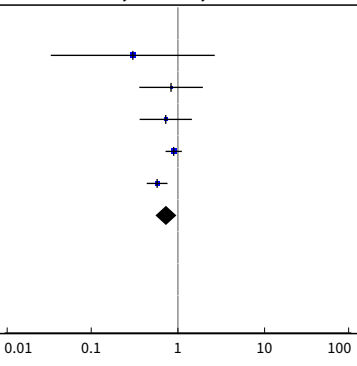
Analysis 2.3. Comparison 2 Intervention comparisons and interactions, Outcome 3 Severe vs less-severe hypoxaemia: longer-term mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Severe hypoxaemia					
Gattinoni 2001	35/53	35/46		11.73%	0.87[0.67,1.12]
Guerin 2004	53/90	49/75		12.13%	0.9[0.71,1.14]
Mancebo 2006	22/43	21/29		8.62%	0.71[0.49,1.02]
Chan 2007	2/6	6/7		1.55%	0.39[0.12,1.25]
Fernandez 2008	5/9	2/4		1.63%	1.11[0.36,3.48]
Taccone 2009	39/73	48/76		11.08%	0.85[0.64,1.11]
Guerin 2013	56/237	94/229		11.02%	0.58[0.44,0.76]
Subtotal (95% CI)	**511**	**466**		**57.76%**	**0.77[0.65,0.92]**
Total events: 212 (Experimental), 255 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=9.81, df=6(P=0.13); I^2=38.85%					
Test for overall effect: Z=2.99(P=0)					
2.3.2 Less severe hypoxaemia					
Gattinoni 2001	57/95	52/103		11.73%	1.19[0.92,1.53]
Guerin 2004	126/323	110/302		13.24%	1.07[0.88,1.31]
Mancebo 2006	16/33	13/31		5.43%	1.16[0.67,1.99]
Chan 2007	3/4	0/4		0.32%	7[0.47,103.27]
Fernandez 2008	3/12	7/12		1.77%	0.43[0.14,1.28]
Taccone 2009	40/93	43/96		9.75%	0.96[0.7,1.33]
Subtotal (95% CI)	**560**	**548**		**42.24%**	**1.07[0.92,1.26]**
Total events: 245 (Experimental), 225 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=5.74, df=5(P=0.33); I^2=12.95%					
Test for overall effect: Z=0.89(P=0.37)					
Total (95% CI)	**1071**	**1014**		**100%**	**0.88[0.76,1.03]**
Total events: 457 (Experimental), 480 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=26.6, df=12(P=0.01); I^2=54.88%					
Test for overall effect: Z=1.63(P=0.1)					
Test for subgroup differences: Chi^2=7.79, df=1 (P=0.01), I^2=87.16%					



Analysis 2.4. Comparison 2 Intervention comparisons and interactions, Outcome 4 Lower tidal volume (TV) ventilation vs higher TV ventilation: longer-term mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Lower TV - mean 6 to 8 mL/kg IBW					
Voggenreiter 2005	1/21	3/19		0.57%	0.3[0.03,2.66]
Chan 2007	5/11	6/11		3.38%	0.83[0.36,1.94]
Fernandez 2008	8/21	10/19		4.71%	0.72[0.36,1.45]
Taccone 2009	79/169	91/174		17.83%	0.89[0.72,1.11]
Guerin 2013	56/237	94/229		14.91%	0.58[0.44,0.76]
Subtotal (95% CI)	**459**	**452**		**41.41%**	**0.73[0.55,0.96]**
Total events: 149 (Experimental), 204 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=7.05, df=4(P=0.13); I^2=43.23%					
Test for overall effect: Z=2.25(P=0.02)					



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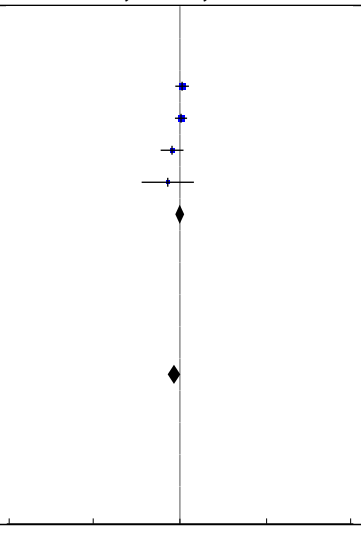
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.2 High TV - mean > 8 mL/kg IBW					
Gattinoni 2001	96/153	90/152		19.56%	1.06[0.89,1.27]
Guerin 2004	179/413	159/378		20.44%	1.03[0.88,1.21]
Mancebo 2006	38/76	37/60		13.88%	0.81[0.6,1.1]
Fernandez 2008	8/21	10/19		4.71%	0.72[0.36,1.45]
Subtotal (95% CI)	**663**	**609**		**58.59%**	**1[0.88,1.12]**
Total events: 321 (Experimental), 296 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.24, df=3(P=0.36); I^2=7.37%					
Test for overall effect: Z=0.08(P=0.94)					
Total (95% CI)	**1122**	**1061**		**100%**	**0.85[0.72,1.01]**
Total events: 470 (Experimental), 500 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=18.34, df=8(P=0.02); I^2=56.38%					
Test for overall effect: Z=1.85(P=0.06)					
Test for subgroup differences: Chi^2=4.15, df=1 (P=0.04), I^2=75.93%					

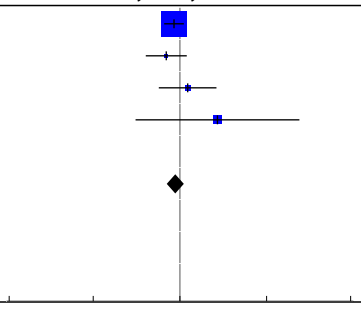


Comparison 3. Pneumonia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pneumonia	4	1007	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.71, 1.11]

Analysis 3.1. Comparison 3 Pneumonia, Outcome 1 Pneumonia.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Guerin 2004	85/413	91/378		79.33%	0.85[0.66,1.11]
Voggenreiter 2005	10/21	13/19		11.4%	0.7[0.4,1.2]
Mancebo 2006	14/76	9/60		8.4%	1.23[0.57,2.64]
Fernandez 2008	3/21	1/19		0.88%	2.71[0.31,23.93]
Total (95% CI)	**531**	**476**		**100%**	**0.88[0.71,1.11]**
Total events: 112 (Experimental), 114 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.54, df=3(P=0.47); I^2=0%					
Test for overall effect: Z=1.06(P=0.29)					



Comparison 4. Duration of mechanical ventilation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of mechanical ventilation	3	871	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-1.53, 0.59]

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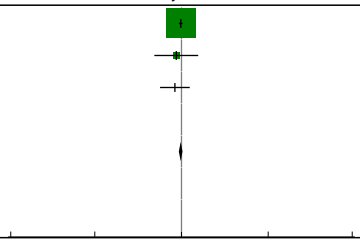
Analysis 4.1. Comparison 4 Duration of mechanical ventilation, Outcome 1 Duration of mechanical ventilation.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Guerin 2004	413	13.7 (7.8)	378	14.1 (7.6)		97.76%	-0.4[-1.47,0.67]
Voggenreiter 2005	21	30 (17)	19	33 (23)		0.71%	-3[-15.64,9.64]
Fernandez 2008	21	11.9 (9.2)	19	15.7 (16.9)		1.54%	-3.8[-12.36,4.76]
Total ***	**455**		**416**			**100%**	**-0.47[-1.53,0.59]**

Heterogeneity: Tau^2=0; Chi^2=0.75, df=2(P=0.69); I^2=0%

Test for overall effect: Z=0.87(P=0.38)



Comparison 5. Length of stay (LOS)

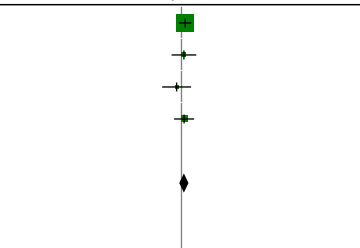
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ICU LOS	4	1309	Mean Difference (IV, Fixed, 95% CI)	1.37 [-1.29, 4.04]

Analysis 5.1. Comparison 5 Length of stay (LOS), Outcome 1 ICU LOS.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Guerin 2004	413	26.6 (29.6)	378	24.5 (21.9)		54.49%	2.1[-1.51,5.71]
Mancebo 2006	76	20.5 (18.2)	60	19.1 (23.1)		13.94%	1.4[-5.73,8.53]
Fernandez 2008	21	14.7 (9.7)	19	17.5 (16.1)		10.19%	-2.8[-11.14,5.54]
Taccone 2009	168	17.5 (29.7)	174	16 (24.3)		21.37%	1.5[-4.26,7.26]
Total ***	**678**		**631**			**100%**	**1.37[-1.29,4.04]**

Heterogeneity: Tau^2=0; Chi^2=1.12, df=3(P=0.77); I^2=0%

Test for overall effect: Z=1.01(P=0.31)



Comparison 6. Mean change in PaO_2/FIO_2 quotient (mmHg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean increase in PaO_2/FIO_2 quotient (mmHg) at 7 or 10 days	4	827	Mean Difference (IV, Fixed, 95% CI)	24.03 [13.35, 34.71]
1.1 Change data provided	2	268	Mean Difference (IV, Fixed, 95% CI)	16.71 [0.11, 33.32]
1.2 Calculated change data	2	559	Mean Difference (IV, Fixed, 95% CI)	29.19 [15.24, 43.14]

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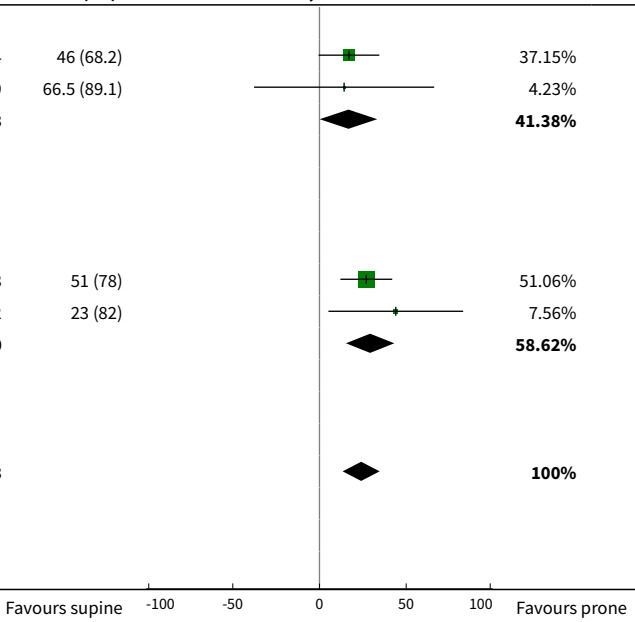
Analysis 6.1. Comparison 6 Mean change in PaO_2/FIO_2 quotient (mmHg), Outcome 1 Mean increase in PaO_2/FIO_2 quotient (mmHg) at 7 or 10 days.

Study or subgroup	Prone N	Prone Mean(SD)	Supine N	Supine Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.1.1 Change data provided							
Gattinoni 2001	114	63 (66.8)	114	46 (68.2)		37.15%	17[-0.52,34.52]
Voggenreiter 2005	21	80.7 (77.3)	19	66.5 (89.1)		4.23%	14.2[-37.74,66.14]
Subtotal ***	**135**		**133**			**41.38%**	**16.71[0.11,33.32]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%							
Test for overall effect: Z=1.97(P=0.05)							
6.1.2 Calculated change data							
Guerin 2004	254	78 (91)	238	51 (78)		51.06%	27[12.05,41.95]
Mancebo 2006	35	67 (80)	32	23 (82)		7.56%	44[5.15,82.85]
Subtotal ***	**289**		**270**			**58.62%**	**29.19[15.24,43.14]**
Heterogeneity: Tau^2=0; Chi^2=0.64, df=1(P=0.42); I^2=0%							
Test for overall effect: Z=4.1(P<0.0001)							
Total ***	**424**		**403**			**100%**	**24.03[13.35,34.71]**
Heterogeneity: Tau^2=0; Chi^2=1.92, df=3(P=0.59); I^2=0%							
Test for overall effect: Z=4.41(P<0.0001)							
Test for subgroup differences: Chi^2=1.27, df=1 (P=0.26), I^2=21.36%							

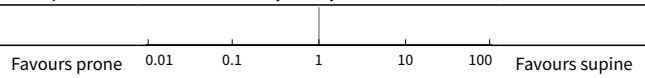


Comparison 7. Adverse events

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Adverse events	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pressure sores	3	366	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.05, 1.79]
1.2 Tracheal tube displacement	8	2021	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.85, 1.39]
1.3 Tracheal tube obstruction	3	1597	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.35, 2.18]
1.4 Pneumothorax	4	664	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.65, 2.08]
1.5 Arrhythmias	3	642	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.47, 0.87]

Analysis 7.1. Comparison 7 Adverse events, Outcome 1 Adverse events.

Study or subgroup	Prone n/N	Supine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 Pressure sores					



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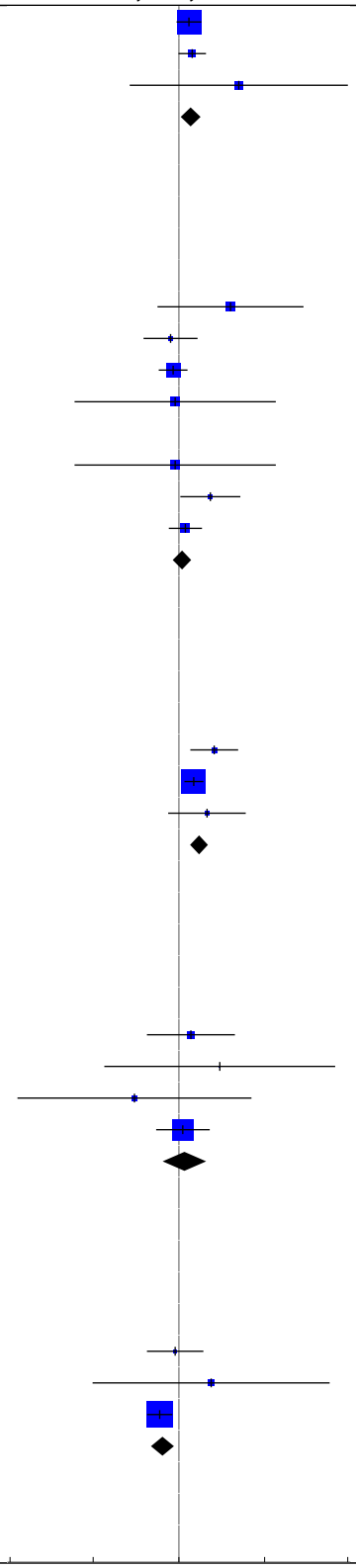
Study or subgroup	Prone n/N	Supine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gattinoni 2001	55/152	42/152		76.23%	1.31[0.94,1.83]
Voggenreiter 2005	19/21	12/19		22.87%	1.43[0.99,2.07]
Chan 2007	2/11	0/11		0.91%	5[0.27,93.55]
Subtotal (95% CI)	**184**	**182**		**100%**	**1.37[1.05,1.79]**
Total events: 76 (Prone), 54 (Supine)					
Heterogeneity: Tau²=0; Chi²=0.88, df=2(P=0.65); I²=0%					
Test for overall effect: Z=2.31(P=0.02)					
7.1.2 Tracheal tube displacement					
Leal 1997	4/8	1/8		0.95%	4[0.56,28.4]
Gattinoni 2001	12/152	15/152		14.21%	0.8[0.39,1.65]
Guerin 2004	44/413	47/378		46.5%	0.86[0.58,1.26]
Voggenreiter 2005	1/21	1/19		0.99%	0.9[0.06,13.48]
Chan 2007	0/11	0/11			Not estimable
Fernandez 2008	1/21	1/19		0.99%	0.9[0.06,13.48]
Taccone 2009	18/168	8/174		7.45%	2.33[1.04,5.21]
Guerin 2013	37/237	30/229		28.91%	1.19[0.76,1.86]
Subtotal (95% CI)	**1031**	**990**		**100%**	**1.09[0.85,1.39]**
Total events: 117 (Prone), 103 (Supine)					
Heterogeneity: Tau²=0; Chi²=7.48, df=6(P=0.28); I²=19.78%					
Test for overall effect: Z=0.65(P=0.52)					
7.1.3 Tracheal tube obstruction					
Guerin 2004	34/413	12/376		16.61%	2.58[1.36,4.91]
Taccone 2009	85/168	59/174		76.66%	1.49[1.16,1.93]
Guerin 2013	11/237	5/229		6.73%	2.13[0.75,6.02]
Subtotal (95% CI)	**818**	**779**		**100%**	**1.72[1.35,2.18]**
Total events: 130 (Prone), 76 (Supine)					
Heterogeneity: Tau²=0; Chi²=2.85, df=2(P=0.24); I²=29.86%					
Test for overall effect: Z=4.44(P<0.0001)					
7.1.4 Pneumothorax					
Mancebo 2006	7/76	4/60		22.62%	1.38[0.42,4.5]
Chan 2007	1/11	0/11		2.53%	3[0.14,66.53]
Fernandez 2008	0/21	1/19		7.95%	0.3[0.01,7.02]
Guerin 2013	15/237	13/229		66.9%	1.11[0.54,2.29]
Subtotal (95% CI)	**345**	**319**		**100%**	**1.16[0.65,2.08]**
Total events: 23 (Prone), 18 (Supine)					
Heterogeneity: Tau²=0; Chi²=1.16, df=3(P=0.76); I²=0%					
Test for overall effect: Z=0.49(P=0.62)					
7.1.5 Arrhythmias					
Voggenreiter 2005	8/21	8/19		10.75%	0.9[0.42,1.93]
Mancebo 2006	1/76	0/60		0.71%	2.38[0.1,57.32]
Guerin 2013	42/237	68/229		88.53%	0.6[0.43,0.84]
Subtotal (95% CI)	**334**	**308**		**100%**	**0.64[0.47,0.87]**
Total events: 51 (Prone), 76 (Supine)					
Heterogeneity: Tau²=0; Chi²=1.61, df=2(P=0.45); I²=0%					
Test for overall effect: Z=2.81(P=0)					



Favours prone — Favours supine

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APPENDICES

Appendix 1. Search strategy for MEDLINE and EMBASE

Search number	Search terms
#1	respiratory insufficiency.mp. or exp Respiratory Failure/
#2	acute respiratory failure.mp. or exp Acute Respiratory Failure/
#3	exp ards/
#4	ards.mp. or exp Adult Respiratory Distress Syndrome/
#5	acute respiratory distress syndrome.mp. or exp Adult Respiratory Distress Syndrome/
#6	lung injury.mp. or exp Lung Injury/
#7	exp Pneumonia/ or pneumon$.mp.
#8	pneumonitis.mp. or exp Pneumonia/
#9	exp aspiration pneumonitis/
#10	pulmonary embolism.mp. or exp Lung Embolism/
#11	exp pulmonary edema/
#12	exp Cardiogenic Shock/ or exp Lung Edema/ or pulmonary oedema.mp.
#13	left ventricular failure.mp. or exp Heart Left Ventricle Failure/
#14	cardiac failure.mp. or exp Heart Failure/
#15	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16	prone.mp.
#17	exp prone position/
#18	prone posit$.mp.
#19	prone position.mp.
#20	prone positioning.mp.
#21	positioning in.mp.
#22	#16 or #17 or #18 or #19 or #20 or #21
#23	ventilat$.mp.
#24	critical care.mp. or exp Intensive Care/
#25	respiratory care.mp. or exp Respiratory Care/

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(Continued)

#26	#23 or #24 or #25
#27	#15 and #22 and #26

Appendix 2. Search strategy for LILACS via the Virtual Health Library, CENTRAL and CINAHL

Search number	Search terms
#1	ARDS or acute respiratory distress syndrome or adult respiratory distress syndrome
#2	Pneumonia
#3	Pneumonitis
#4	Aspiration pneumonitis
#5	Respiratory failure
#6	Respiratory insufficiency
#7	Pulmonary edema
#8	Pulmonary embolism
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	Prone
#11	#9 and #10

Appendix 3. Original data extraction form

DATA EXTRACTION FORM – PRONE POSITION FOR ACUTE RESPIRATORY FAILURE IN ADULTS

(CARG 038)

Reviewer name
Study author & date
Journal, volume, pages & MEDLINE ID
Title
Location of study
Enrolment finished (month & year)
Period of study

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Verification of study eligibility:

	Yes/No	Query or comments
Is this a randomized controlled trial?		
All patients are adults and required mechanical ventilation for acute respiratory failure?		
Relevant clinical outcomes?		

Study population:

Population description	
Inclusion criteria	
Exclusion criteria	

PARTICIPANTS:

Number of eligible participants	Number enrolled in study
Number of males	Number of females

STUDY POPULATION:

Baseline characteristics	Intervention group	Control group	Overall
Number for which data are given			
Sex			
Age (range, mean, SD)			

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(Continued)

SAPS II score
Other severity score (specify)
Number of organ dysfunctions
Organ dysfunction score (specify)
PaO_2
FIO_2
PaO_2/FIO_2
$PaCO_2$
PEEP
PIP
Plat Press
Vt (mL/kg) Unspecified mode - MV Volume controlled Pressure controlled
ALI (%)
ARDS (%)
Pulmonary cause
Extrapulmonary cause
Pneumonia
Shock
Aspiration
Septic shock
Acute on chronic RF
Coma
Postoperative
Non-pulmonary sepsis
Acute cardiogenic pulmonary oedema (%)

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(Continued)

NIV before MV
Number of participants with vasopressors
Planned duration (dose) of prone ventilation (< 18 hours vs > 18 hours/d)
Duration (days) of interventions
Early randomization to prone vs undefined OR late
Severity of process (PaO_2/FIO_2, oxygenation index OR LIS)
CO-INTERVENTIONS
Inhaled nitric oxide
Renal replacement therapy
Packed red cells/participant (units)
Pulmonary artery catheter

Quality of concealment of random allocation:

Allocation was not concealed (e.g. quasi-randomization)	D
Allocation concealment was inadequate	C
Methods of concealment were unclear	B
Concealment was adequate (e.g. numbered, sealed opaque envelopes drawn NON-consecutively)	A
Inclusion and exclusion criteria were not clearly defined in the text	
Outcomes of participants who withdrew or were excluded after allocation were NEITHER detailed separately NOR included in an intention-to-treat analysis	
Outcomes of participants who withdrew or were excluded after allocation were EITHER detailed separately OR included in an intention-to-treat analysis OR the text stated there were no withdrawals	
Treatment and control groups were NOT adequately described at entry	
Treatment and control groups were adequately described at entry. A minimum of 4 admission details were described	

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METHODS:

	Yes	No	Unclear
Subject - blinded (N/A – sedated)	----------	----------	----------
Physician - blinded (N/A - impossible to achieve, as body position cannot be concealed)	----------	----------	----------
Outcome assessor - blinded			

Modified Jadad quality assessment tool (see Appendix for guidance*):

	Yes/No (Y = 1)	Points
1. Was the study described as randomized?		
2. Was the study described as blinded for assessments?		
3. Was there a description of withdrawals?		
Additional point if study randomization appropriate*		
Deducted point if study randomization inappropriate*		

Total points _____

*Give **one additional point** if: For question 1, the method used to generate the sequence was described, and it was appropriate (table of random numbers, computer-generated, etc.)

Deduct one point if: For question 1, the method used to generate the sequence of randomization was described, and it was inappropriate (participants were allocated alternately or according to date of birth, hospital number, etc.)

RESULTS AND OUTCOMES:

	Intervention group	Control group	Overall
10-Day mortality			
ICU mortality			
28-Day mortality			
Hospital mortality			

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(Continued)

90-Day mortality
Duration of MV
Time to extubation
ICU length of stay
Hospital LOS
Days with ARDS
Days with ALI
Days with LIS > 2
VAP rate
Percentage of participants with VAP/Prevalence of pneumonia
Days on vasopressors
FIO_2 d4
PaO_2 d4
PaO_2/FIO_2 d4
$PaCO_2$ d4
Vt d4
FIO_2 d10
PaO_2 d10
PaO_2/FIO_2 d10
$PaCO_2$ d10
Vt d10
Economic evaluation

COMPLICATIONS:

	Intervention group	Control group	Overall

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(Continued)

New pressure sores
Arrhythmias
Pneumothorax
Unplanned extubation/“Displacement” of tracheal tube/Obstruction
Intracranial hypertension
Total number of complications documented for both groups

SUB-GROUP ANALYSES:

	Intervention group	Control group	Overall
10-Day mortality/SAPS > 49			
ICU mortality SAPS > 49			
ICU mortality SAPS ≤ 49			
ICU or 10-day mortality according to SAPS cutoffs			
Vt ≥ 12 mL/kg			
$PaO_2/FIO_2 \leq 88$			

WHAT'S NEW

Date	Event	Description
13 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving of the review: Roxanna Bloomfield (RB), David W. Noble (DWN).
Co-ordinating the review: RB, DWN.
Undertaking manual searches: RB, DWN.
Screening search results: RB, DWN.
Organizing retrieval of papers: RB, DWN.
Screening retrieved papers against inclusion criteria: RB, DWN.
Appraising quality of papers: RB, DWN, Alexis Sudlow (AS).
Abstracting data from papers: RB, DWN, AS.
Writing to authors of papers for additional information: DWN.
Providing additional data about papers:

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Obtaining and screening data on unpublished studies: RB, DWN.
Managing data for the review: RB, DWN.
Entering data into Review Manager (RevMan 5.3): RB, DWN, AS.
Analysing RevMan statistical data: DWN.
Performing other statistical analyses not using RevMan:
Performing double entry of data: (data entered by person one: RB; data entered by person two: DWN).
Interpreting data: RB, DWN, AS.
Making statistical inferences: RB, DWN.
Writing the review: RB, DWN, AS.
Securing funding for the review:
Performing previous work that served as the foundation of the present study:
Serving as guarantor for the review (one review author): DWN.
Taking responsibility for reading and checking the review before submission: RB.

DECLARATIONS OF INTEREST

Roxanna Bloomfield: none known.

David W Noble: none known.

Alexis Sudlow: none known.

SOURCES OF SUPPORT

Internal sources

- NHS Grampian, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the protocol (Bloomfield 2009).

- We replaced Nigel Webster, who had insufficient time to assist with the review process, with Alexis Sudlow.
- We added references and Background text.
- We made the definition of tidal volume more specific for the purpose of identifying studies that employed "lung-protective ventilation" (i.e. tidal volume should be expressed in mL per kg of *ideal* body weight.
- Risk of bias methods for a Cochrane review have changed since protocol publication, and we reanalysed data for the new format.
- The GRADE-based summary of findings table has been introduced since protocol publication, and we have therefore retrospectively chosen the analyses displayed.
- We did not employ the Q-partitioning method (Deeks 2011) in exploring heterogeneity.
- We made minor modifications to search strategies for Ovid MEDLINE, EMBASE, CENTRAL, CINAHL and LILACS to better suit their updated search engines.
- We changed the cutoff for prolonged duration of prone positioning from 18 or more hours per day to 16 or more hours per day. This placed the last published study (Guerin 2013) in the more biologically appropriate category for analysis. (The mean duration of proning in the short-duration proning group was 8.3 hours per day, and for the long-duration proning group 18.1 hours per day, and one study aiming for 20 hours per day actually achieved 17 hours per day (Mancebo 2006). The study of Guerin et al (Guerin 2013) also achieved proning for a mean of 17 hours per day.)

INDEX TERMS

Medical Subject Headings (MeSH)

*Prone Position; Acute Disease; Hypoxia [etiology] [mortality] [therapy]; Patient Positioning [*methods] [mortality]; Randomized Controlled Trials as Topic; Respiration, Artificial [*methods] [mortality]; Respiratory Distress Syndrome, Adult [mortality] [*therapy]; Respiratory Insufficiency [mortality] [*therapy]

MeSH check words

Adult; Humans; Middle Aged

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